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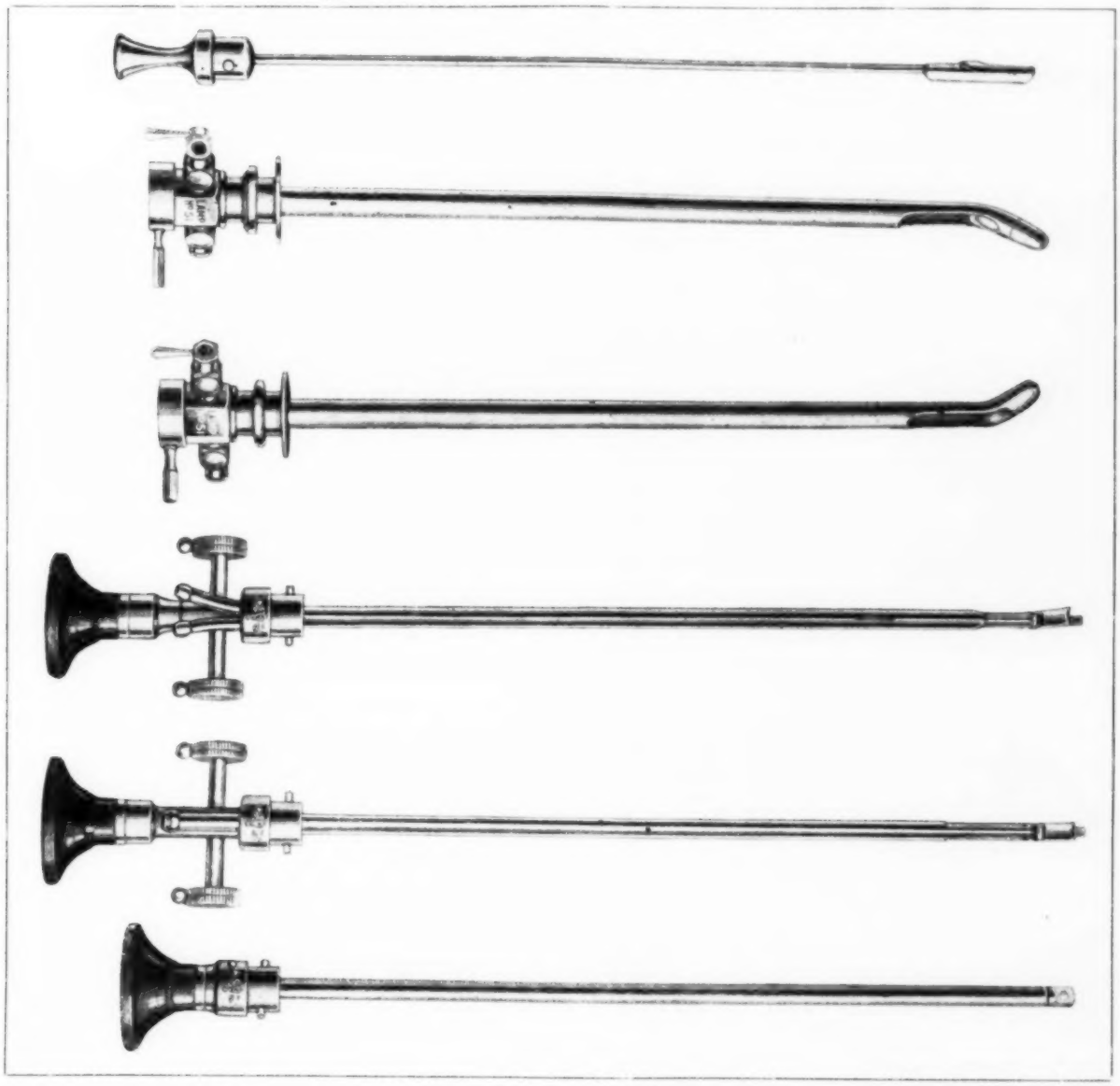

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VAN DIE REDAKSIE

CORTISONE EN ACTH

In hierdie uitgawe begin die publikasie van die bydraes gelewer op een van die voltallige sittings van die Mediese Kongress wat in September 1952 in Johannesburg gehou is. Lesers sal onthou dat die simposium gehandel het oor die toepassing van die pituitêre adrenokortikotropiese hormoon (ACTH) en die adrenokortikale hormone (cortisone en hydrocortisone). Die verhandelinge vorm 'n nuttige bydrae tot bestaande kennis omtrent die kliniese waarde van hierdie preparate.

Baie van die waarnemings wat deur werkers in ander dele van die wêreld gemaak is, word bevestig; en in 'n aantal gevalle word aanspraak vir die eerste maal van 'n geneeskundige uitwerking gemaak, b.v. subakute bakteriese endocarditis, long-embolie, irriterende gasvergiftiging van die longe, tydelike steuring van die onderkaakgewrig en trigeminale en atipiese gesigsenuweepyne.

Hormone (b.v. adrenaline, thyroxine, insulin en die geslagsteroïde) was vir baie jare met behandeling gebruik, maar op baie beperkte skaal, en was meesal beperk tot die verbetering van 'n spesifieke tekortkoming, of om onderdrukkingsuitwerkings te bewerkstellig. Later was dit besef dat die geslagshormone, benewens hulle spesifieke uitwerking, op sekere metaboliese prosesse 'n beperkte invloed uitoefen. Behalwe hulle welbekende konvensionele uitwerkings het ACTH en die adrenokortikalesteroïde 'n invloed op die liggaam se verdedigingsmeganisme teen spanning. In hierdie sin vorm hulle 'n basiese faktor in die Algemene Aanpassingsindroom en die Spanningsteorie van Siekte wat deur Selye aangebied word.

Met die invoering van hierdie hormone het ons seer sekerlik 'n nuwe era in geneeskunde en medisyne binnegegaan. Tot hier toe was die geveg teen siekte gebaseer op die poging om die siektekiem te vernietig, te neutraliseer of te elimineer, hetsy dit van bakteriese gifstof of chemiese gif is. Ons pogings om die uitwerkings van

EDITORIAL

CORTISONE AND ACTH

In this issue we begin the publication of the contributions made to one of the plenary sessions of the Medical Congress held in Johannesburg in September 1952. Readers will recall that the symposium dealt with the application of the pituitary adrenocorticotrophic hormone (ACTH) and the adrenocortical hormones (cortisone and hydrocortisone). The papers form a useful addition to existing knowledge about the clinical value of these preparations.

Many of the observations made by workers in other parts of the world are confirmed, and a therapeutic effect of these hormones is claimed for the first time in a number of conditions, e.g. subacute bacterial endocarditis, pulmonary embolism, irritant gas poisoning of the lungs, temporo-mandibular joint derangements and trigeminal and atypical facial neuralgias.

Hormones (e.g. adrenaline, thyroid, insulin and the sex steroids) have been used in treatment for many years, but in a fairly limited way, and confined in the main to correcting a specific deficiency or producing suppressive effects. More recently it has been appreciated that the sex hormones exert a limited influence on certain metabolic processes, in addition to their specific effects. ACTH and the adrenocortical steroids, apart from their well-known conventional effects, have an influence on the defence mechanisms of the body against stress. In this sense they constitute a basic factor in the General Adaptation Syndrome and the Stress Theory of Disease propounded by Selye.

With the introduction of these hormones we have undoubtedly entered a new era in therapeutics and medi-

besering te keer was baie beperk; maar met hierdie nuwe wapens gebruik ons heeltemal 'n ander krygslis. Hierdie hormone help die liggaam teen invalle en trauma, d.w.s. die nadruk is op die verdedigingsmeganisme van die slagoffer liewer as op 'n aanslag op die siektekiem, ongeag die aard daarvan. Dit is derhalwe verstaanbaar dat ons nou sukses mag hê, selfs wanneer die werklike oorsaak van die siekte onbekend is. Die manier van optrede sal die waarde van die hormone by die beheer en behandeling van 'n groot verskeidenheid van oënskynlik nie-verwante toestande verduidelik, en die indruk skep dat hulle 'n aansienlike wye nie-spesifieke omvang van aksie het. Aangesien hulle biologiese uitwerkings wyd versprei is en nie spesifiek op enige enkel liggaamsfunksie gemik is nie, kan hierdie middels nie as kuratief beskou word nie, hoewel hulle tydige gebruik onder sekere omstandighede lewens mag red.

Dit moet beklemtoon word dat hulle natuurlike biologiese produkte is, en hoewel hulle invloed op die liggaam dikwels baie diepgaande is, is hulle uitwerking nogtans fisiologies van aard, aangesien hulle 'n vergroting of vermindering van normale metaboliese prosesse voortbring. Die uitwerking duur egter net gedurende die tydperk van toediening, en vir 'n kort tydjie nadat daarmee opgehou word. Dit is hierdie eienskap wat hulle (soos alle ander hormone) in 'n unieke kategorie plaas, beslis verskillend van baie ander terapeutiese stowwe, b.v. die antibiotiese preparate, anti-skildklier- en anti-rumatiekpreparate, wat vreemd is aan die liggaamsekonomie en, derhalwe, die weefsel blootstel aan hulle giftige, vernietigende en hiperergiese uitwerkings, wat lei tot onwenslike veranderings van weefsel, wat ten spyte van staking van behandeling dikwels nie ongedaan gemaak kan word nie. Ondervinding het geleer dat geen slegte nagevolge van 'n permanente aard sover by pasiënte wat ACTH of cortisone voortdurend vir lang tydperke ontvang het, opgemerk is nie. Weens hierdie rede, het dr. M. M. Suzman die standpunt ingeneem dat die besorgdheid wat uitgespreek is oor die inherente gevare van hierdie vorm van behandeling vergroot mag gewees het, en dat ongelukkige bygevolge, met behoorlike voorsorg, in die meederheid van gevalle voorkom kan word. Dit lyk ook of laboratoriumbeheer, by die gemiddelde geval, grootliks oorbodig is—'n belangrike praktiese oorweging.

'n Studie van die biologiese uitwerkings van hierdie hormone tydens gesondheid en siekte is vinnig besig om 'n beter begrip, nie net van die funksies van die liggaam nie, maar ook van die aard van siekte, teweeg te bring. Die onlangse besef van die menigvuldige maniere waarop die hormone onder bespreking liggaamlike funksie en aktiwiteit beïnvloed, het 'n verskillende algemene benadering van die probleme van geneeskunde tot gevolg gehad, maar een wat nie met teorië wat voorheen voorgelê is en waarby dit geïntegreer kan word, bots nie.

Ons begrippe van medisyne en die onderrig daarvan staan op die drumpel van groot en fundamentele veranderings.

cine. Hitherto the fight against disease has been based on the attempt to destroy, neutralize or eliminate the pathogen, whether it be bacterial toxin or chemical poison. Our attempts to reverse the effects of injury have been very limited; but with these new weapons we employ an entirely different therapeutic stratagem. These hormones aid the body in its defence against invasion and trauma, i.e. the emphasis is on the defence mechanisms of the host rather than on an assault upon the pathogen, irrespective of its nature. It is, therefore, understandable that we may now meet with success even when the actual cause of the disease is unknown. The mode of action will explain the value of the hormones in the control and treatment of a great variety of seemingly unrelated conditions and create the impression that they have a fairly wide non-specific range of action. As their biological effects are widespread and not specifically directed to any one bodily function, these agents cannot be considered curative, although in certain conditions their timely use may prove life-saving.

It should be stressed that they are natural biological products and although their influence on the body is often very profound, their action is, nevertheless, physiological in type, as they produce an exaggeration or a diminution of normal metabolic processes. The effects, however, persist only during the period of administration, and for a short time after their withdrawal. It is this characteristic which places them (in common with all other hormones) in a unique category distinctly different from many other therapeutic agents, e.g. the antibiotics and anti-thyroid and anti-rheumatic preparations, which are foreign to the body economy and may, therefore, expose the tissues to their toxic, destructive or hyperergic effects, leading to undesirable tissue changes, often irreversible despite the cessation of therapy. Experience has shown that no ill effects of a permanent nature have been observed so far in patients who have received ACTH or cortisone continuously for prolonged periods. For this reason Dr. M. M. Suzman took the view that the fears expressed about the inherent dangers of this form of treatment may have been exaggerated, and that with proper precautions untoward side-effects may be prevented in the majority of cases. It also seems likely that laboratory control is largely superfluous in the average case—an important practical consideration.

A study of the biological effects of these hormones in health and disease is rapidly producing a better understanding not only of the functions of the body but also of the nature of disease. The recent appreciation of the multitudinous ways in which the hormones under discussion influence bodily function and activity has given rise to a different general approach to the problems of medicine, but one not in conflict with theories previously propounded and into which it can be integrated.

Our concepts of medicine and its teaching are on the brink of vast and fundamental changes.

THE CLINICAL APPLICATION OF CORTICOTROPIN AND CORTISONE THERAPY

A REPORT OF 247 CASES *

M. M. SUZMAN, M.D. (DURH.), M.R.C.P. (LOND.)
Johannesburg

In the short time that has elapsed since the introduction of corticotropin (ACTH) and cortisone for clinical study, these hormonal agents have already taken their place in therapeutics and a voluminous literature on the subject has appeared. Nevertheless, although their value has been well established in respect of certain conditions, the scope and limitations of this form of therapy has not as yet been defined completely.[1] The historical events which led to the discovery and application of these hormones and to the elucidation of the role of the pituitary and adrenal glands in the genesis and control of disease are too widely documented to be repeated here.[2]

The main purpose of this paper is the presentation of the results obtained with these hormones in a comparatively large series of patients, treated for a wide variety of diseases in the past 3 years. Before proceeding with the case reports, consideration will be given firstly, to the basic physiological principles and the biological effects on which these hormones depend for their therapeutic efficacy; secondly, to the untoward side effects and hazards which may be associated with their use.

PHYSIOLOGICAL CONSIDERATIONS [3]

The pituitary-adrenal axis [3] constitutes, with the nervous system the main integrating mechanism in the defence of the body during stress and is thus intimately bound up, in one way or another, with almost all forms of injurious processes.

The adrenocorticotropic hormone of the anterior pituitary (ACTH) acts exclusively on the adrenal cortex, causing the discharge of adrenocortical hormones into the circulation, at a rate which depends on the functional responsiveness of the adrenal cortex and, within certain limits, on the concentration of ACTH in the blood perfusing the gland. It is thus obvious that with a non-functioning adrenal cortex, as in Addison's disease, the administration of ACTH will be entirely ineffective. Although more than 30 different steroids have been isolated from the adrenal cortex, it has been shown that, after stimulation with ACTH, the blood in the adrenal vein contains principally hydrocortisone (Compound F or 17-hydroxycorticosterone) and corticosterone (Compound B) and only small quantities of the better known steroids, cortisone (Compound E or 11-dehydroxy-17-hydroxy-corticosterone) and desoxycorticosterone. Hydrocortisone is probably the main adrenocortical hormone, as it reproduces almost all the known effects of ACTH itself, but cortisone exerts an effect very similar and is probably converted to hydrocortisone in the body.

It appears that these hormones are utilized quantitatively by the tissues in proportion to the degree of tissue injury present. A reciprocal regulating mechanism exists between the anterior pituitary and the adrenal cortex whereby the activity of the pituitary as regards its ACTH secretion is controlled by the level of circulating adrenocortical steroids, a low blood level increasing its activity and a high level exerting a suppressive effect. Thus, when the body tissues are injured or diseased, the fall in circulating steroids, resulting from their increased utilization, leads to a prompt increase in the elaboration of ACTH by the pituitary, thereby replenishing the adrenocortical steroid content of the blood to meet the increased requirements of these hormones by the peripheral tissues. ACTH secretion is also activated by adrenalin and other humoral agents and also by neurogenic stimuli arising from sites of injured tissues and reaching the pituitary by way of the hypothalmus, thus setting in motion the pituitary-adrenal defence mechanism in the face of sudden situations of stress.

The production of ACTH may be influenced by dietary factors. Optimum levels are maintained by a high protein intake, but it is reduced when the diet lacks protein or contains excessive quantities of carbohydrate.[4]

The administration of exogenous ACTH causes hypertrophy and hyperplasia of the adrenal cortex involving mainly the zona fasciculata and zona reticularis and narrowing of the zona glomerulosa. There is an increase in its secretory activity and depletion of cell lipid.[5] Because of the resulting increased corticoid secretion, endogenous pituitary activity is suppressed. When administration of ACTH is discontinued, regression of the hypertrophied adrenal cortex rapidly occurs and the pituitary resumes its normal level of activity.

On the other hand, the administration of exogenous corticoids, through a suppressive effect on ACTH secretion, induces compensatory atrophy of the adrenal cortex, involving chiefly the zona fasciculata and zona reticularis, and broadening of the zona glomerulosa. There is a reduction in its secretory activity and an accumulation of cell lipid.[5]

This suppressive action of cortisone is of importance and is the basis for its use in controlling syndromes due to adrenocortical hyperplasia. On discontinuation of the cortisone administration, the adrenal cortex regenerates, but will remain relatively unresponsive to ACTH and symptoms of adrenocortical insufficiency may occur until sufficient time has elapsed to allow for its recovery. However, under conditions of overwhelming stress, the resulting high level of endogenous corticoids, supplemented even by the administration of exogenous corticoids, will fail to depress adrenocortical activity, thus ensuring a constant hypersecretion of corticoids to meet the increased requirements of the tissues. In fact, overwhelming stress or overdosage of endogenous ACTH may so overstimu-

* Address delivered at the Plenary Session of the 38th South African Medical Congress, 17th Annual Scientific Meeting, at Johannesburg on 23 September 1952.

late the adrenal cortex that exhaustion of the gland may occur, followed in some instances by necrosis and haemorrhage.

BIOLOGICAL EFFECTS AND MECHANISMS OF ACTION OF ADRENAL CORTICOIDS

A rational approach to the clinical application of ACTH and cortisone is not possible without an appreiation of the biological effects and the mechanisms of action on which they depend for their therapeutic efficacy. The adrenal corticoids exert a widespread effect on the body, acting on many target organs and tissues through different mechanisms and profoundly influence the functional activity of several metabolic systems.[3, 6]

These hormones exert a catabolic or anti-anabolic action on protein metabolism, thereby suppressing the synthesis of proteins, increasing the loss of nitrogenous substances and leading to atrophy of certain cellular tissues. Adrenal corticoids influence carbohydrate metabolism through an anti-insulin effect, thereby reducing glucose tolerance and leading to hyperglycaemia and glycosuria. Fat metabolism is affected in that increased quantities of fat are stored in the liver and other fat depots and ketone production is reduced. Changes in electrolyte and water metabolism occur with a tendency towards retention of sodium and water and an increase in the urinary loss of potassium.

Adrenocorticoids influence the growth and development of certain cells and tissues, exerting an inhibitory effect on some and a stimulating action on others.[7] The formation of eosinophils and lymphocytes is suppressed giving rise to eosinopenia and lymphopenia, whereas the production and delivery of neutrophils and erythrocytes is increased. Through a depressive effect on mitotic division in certain formative cells, these hormones induce involution of thymic and lymphoid tissue (lympholysis) and of certain neoplastic tissues. They suppress the growth of connective and collagen tissue and also induce osteoporosis.

The normal tissue reactions against injurious agents are inhibited by adrenocorticoids without at the same time eliminating, destroying or neutralizing the irritant factor or noxious agent, whether this be a microbe, a toxin or a chemical poison.[8] Similarly, allergic tissue responses, particularly of the delayed cellular type, are suppressed or diminished, whereas the immediate reactions, in which the release of histamine plays an important role, are said not to be affected to the same extent.[9] These corticoids increase capillary resistance[10] and also tend to prevent the formation of exudates and other products of tissue reactivity and to promote their dissipation. Fibroplasia is suppressed, thereby inhibiting the formation of fibrous tissue and the development of subsequent cicatrization. Wound healing may be retarded, but this occurs mainly when excessively high dosage is used or in debilitated, undernourished and protein-depleted subjects.[11] In the role of suppressing tissue reactivity, it is apparent that the action of adrenal corticoids may be regarded as anti-inflammatory, protecting vulnerable tissues against injurious agents.

These hormones also influence the functional activity of other systems. Psychomotor activity is increased[12] and muscular power is augmented. There occurs an increase in gastric secretory activity,[13] in hepatic blood flow and splanchnic oxygen consumption[14] and there is a tendency towards depression of thyroid function,[15] as well as an alteration in the activity of certain other enzyme systems.

SIDE EFFECTS AND HAZARDS OF CORTISONE AND ACTH ADMINISTRATION

During therapy with ACTH or cortisone certain side effects may occur, which are unrelated to the disease under treatment. The development of these manifestations is dependent on the physiological action of the hormones and they tend to occur mainly, but not always, when the dosage is excessive and are more frequently seen in children and young adults. As a rule they may be prevented or controlled by the institution of appropriate measures, but they always disappear, either promptly or slowly, after treatment is discontinued, and no permanent ill effects have been reported.

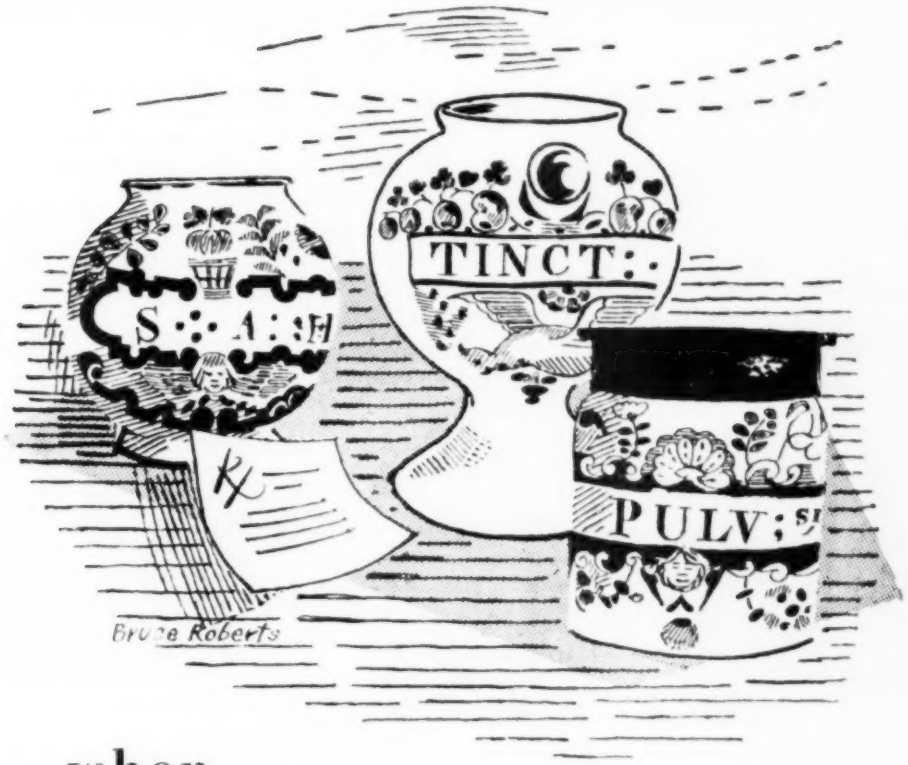
Some of these side effects are undesirable, necessitating measures for their relief, whereas others are of a trivial nature and may be disregarded. The most commonly observed is excessive fluid retention producing varying degrees of oedema. In some cases this may be accompanied by a rise in blood pressure due to an expanding blood volume. Sodium retention is the cause and this may be prevented or controlled by restricting the salt intake and by prescribing substantial amounts of potassium chloride. A high potassium intake tends to limit the retention of sodium and water.[16] In refractory cases of oedema or in those with incipient cardiac failure, the use of mercurial diuretics or cation exchange resins may prove of value.

Due to the increased loss of potassium, signs of hypopotassaemia may occur, such as apathy, lethargy, muscular weakness and cramps, abdominal pains and distention. The onset of these symptoms will call for an increase in the daily ration of potassium chloride, of which 8–12 gm. may be needed to control the symptoms.

Glycosuria and hyperglycaemia may be disregarded unless the patient is diabetic, in which case more insulin may be needed. Tissue wasting and osteoporosis are more apt to occur in elderly patients, in whom instances of spontaneous fractures have been reported.[17] The measures used to prevent or control these complications are the use of a high protein diet and the administration of calcium and anabolic agents, such as androgens and oestrogens.

Due to the androgenic activity of the adrenocorticoids certain hormonal side effects commonly appear, more particularly in children and young adults. These consist of hirsutism, acneiform eruption, rounding of the facies, referred to as 'moon or squirrel face', retrocervical pad of fat ('buffalo hump'), atrophic striae of skin and thinning of the scalp hair. With high dosage, a frank Cushing's syndrome may develop. All these changes are temporary and abate when the hormones are withdrawn.

With prolonged administration, the function of the thyroid gland may be depressed, leading to what is termed 'corticogenic hypothyroidism'.[15] This complication is of importance in that lack of thyroid hormone diminishes the responsiveness not only of the adrenal cortex to



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ACTH, but also of the tissues to cortisone, with the result that the treatment may become ineffective, leading to a gradual return of the symptoms of the disease under treatment and also to an intensification of some of the untoward side effects, such as oedema and hypertension. For the prevention and control of this situation, thyroid medication is needed, particularly in those patients in whom it is anticipated that continuous hormone therapy of long duration will be required. In children and infants on prolonged therapy, retardation of growth may result and to prevent this, careful adjustment of the dosage is essential.

While under treatment with these hormones, most patients exhibit an elevation of spirits and experience an increased sense of well-being. Some become restless, agitated and sleepless, but without showing undue fatigue. Occasional patients may exhibit a marked degree of mental depression or may pass into a frankly psychotic state, resembling schizophrenia, from which they readily emerge, however, shortly after discontinuation of the treatment. As these mental complications are more likely to occur in subjects with a psychopathic personality or in those with a previous history of psychotic episodes, ACTH or cortisone therapy should be precluded in such patients or used with great caution.[18]

Four instances of psychosis induced by ACTH or cortisone were observed in the present series of patients. One case was that of a patient with severe intractable asthma with advanced emphysema, refractory to ACTH and cortisone given in conventional dosage, who developed a schizophrenic-like psychosis when the dosage of ACTH was increased. During the psychotic phase, which lasted for several days after the ACTH had been withdrawn, the asthma ceased completely and there was marked relief of the respiratory embarrassment caused by the emphysema. When the mental disturbance lifted, the extreme dyspnoea due to asthma and emphysema promptly returned.

In this connexion it is of interest that in schizophrenic subjects there is a decrease in reactivity, not only in the emotional, but also in the physical sphere. Consequently they do not suffer from the physical conditions which arise as the result of stress, such as asthma, the allergies, peptic ulcer or hypertension. Asthmatic patients are completely relieved of their asthma when they become schizophrenic, but on recovery the asthma returns. Their responses to stress are markedly reduced as judged by pituitary-adrenocortical function, whereas their tissue responses to adrenal corticoids are normal.[19] It would seem that the study of the role of endocrine inter-relationships offers a fertile field for future research in mental disease.

Certain hazards are said to be connected with ACTH and cortisone therapy. The occurrence of haemorrhage or perforation in patients with peptic ulceration[20] and the reactivation of latent pulmonary tuberculosis have been reported.[21] That the hormonal agents were the sole precipitating factors in the development of these complications is, to my mind, not fully established, the element of chance not having been excluded. Yet, caution is advised in the use of this form of treatment for patients suffering from or with a history of these ailments.

Deep-seated infections or an abdominal catastrophe may remain undetected because of the masking effect that these hormones exert on the symptoms of inflammation. A difficult diagnostic problem may arise in such circumstances.

Experience shows that when patients receiving cortisone or ACTH are in need of a surgical operation, the treatment need not be discontinued; but rather, the dosage should be increased for a few days, to enable the patient the better to withstand the additional stress of surgery.[22] Wound healing as a rule, is not retarded, except in debilitated, protein-depleted patients.

In respect of the well-being of both mother and child, there appears to be no reason to withhold cortisone or ACTH during pregnancy or parturition,[23] provided the necessary precautions are taken to prevent the onset of undesirable side effects, particularly those pertaining to salt retention.

CLINICAL EXPERIENCES

My first clinical experience in the use of this form of therapy took place in July 1949, when an early preparation of ACTH (Organon) was administered for a short period to a young woman gravely ill with acute systemic lupus erythematosus. The improvement observed was distinct though temporary. With the same preparation administered for several days, a dramatic response was obtained in a patient with advanced rheumatoid arthritis, the improvement unexpectedly persisting for several months.

In April 1950, having received our first supply of Cortisone * for investigative purposes, a comprehensive clinical and biochemical study was instituted in collaboration with Dr. B. Bloomberg and Dr. R. Bernstein, in a series of 9 patients, consisting of 3 cases each of rheumatoid arthritis and acute leukaemia, and one case each of Still's disease, advanced gouty arthritis and acute cholaemic viral hepatitis.

The laboratory investigations included serial complete blood counts and eosinophil counts, and serial determinations of the electrolytes, sodium, potassium and chlorides, and of the erythrocyte sedimentation rate (Wintrobe), blood proteins, including gamma globulin, the sheep cell agglutination test (Rose), anti-streptolysin-O-titre, thymol turbidity, thymol flocculation, the cephalin-cholesterol-flocculation, Takata-Ara, uric acid, uric acid-like substances and cholesterol, as well as the 24-hour excretion of uric acid, creatinine and neutral 17-ketosteroids.

The details of these observations form the subject of a separate communication.[24]

Between July 1949 and August 1952, over 250 patients have been treated with ACTH and/or cortisone, and of these 247 form the subject of this report. The numbers of cases in each disease group and the treatment received are shown in Table 1. Approximately one-half of this number received treatment at the Johannesburg General Hospital in collaboration with Dr. B. Goldberg. In most cases the patients were hospitalized for the initial course of therapy, but those not severely ill were treated throughout as out-patients. Where possible, all other medication was omitted, except in a few instances in which observations were made concerning the combined use of either ACTH or cortisone with other therapeutic agents, such as androgens, para-amino-benzoic acid and desiccated thyroid. For the prevention of untoward side effects, the measures already referred to were adopted in all cases.

* The Cortisone acetate (Cortone, Merck) was supplied for research purposes through the courtesy of Dr. J. M. Carlisle, Medical Director, Merck & Co., Inc., Rahway, N.J., U.S.A.

TABLE I: SHOWING THE NUMBERS OF CASES IN VARIOUS DISEASE-GROUPS TREATED WITH ACTH AND/OR CORTISONE IN THE PERIOD JULY 1949 TO AUGUST 1952.

Disease Groups	*ACTH*	*Cortisone*	*Cortisone and ACTH*	*Total*
Rheumatic and Arthritic Diseases	18	34	18	70
Collagen Diseases ..	8	6	9	23
Pulmonary Conditions	18	15	9	42
Liver Diseases	8	—	2	10
Neuro-Psychiatric Conditions	11	8	2	21
Endocrine Disorders ..	—	5	—	5
Metabolic Disorders ..	6	5	2	13
Eye Diseases	1	5	1	7
Skin Diseases	3	2	4	9
Peripheral Vascular Diseases	3	—	—	3
Blood Disorders ..	1	1	4	6
Leukaemias	4	4	2	10
Neoplastic Diseases ..	6	6	4	16
Miscellaneous Conditions	8	2	2	12
Totals	94	94	59	247

CHOICE OF MEDICATION

On the whole, no special reasons determined the use of ACTH or cortisone in any particular case, except where it was known or suspected that the adrenal cortex would be unresponsive, or in hypertensive patients, when cortisone was preferred. In many instances patients were given courses of ACTH and cortisone alternately, in an attempt to determine which was the more effective. In several instances, and for no apparent reason, whereas a satisfactory result was obtained with the one preparation, little or no response could be obtained with the other. ACTH alone was used in 94 patients, cortisone alone in 94 and both agents at different times in 59 patients (Table I).

METHODS OF ADMINISTRATION AND DOSAGE

ACTH

At first, ACTH was administered by intermittent intramuscular injection at intervals of 6 or 8 hours, but later the subcutaneous route was used and this was found to be at least as effective and more convenient. By these routes the required daily dose of ACTH has varied widely in different patients and for different conditions. For initial suppression of the disease, from 40 to 120 International Units (I.U.) has usually been found necessary; for effective maintenance, a daily dosage of 10 to 40 units in at least 2 divided doses has been required, although in some diseases much larger doses were needed.

During the past 12 months, wide use has been made of continuous intravenous infusions of from 10 to 30 units of ACTH in dextrose water, given daily over a period of 8 or more hours. It has been shown that with amounts greater than this no further response can be elicited.[25] This is the most effective and economical means of administering ACTH and is the method of choice for all seriously ill patients in need of ACTH, where a prompt response is desirable. ACTH administered intravenously has proved effective when no response was obtained by other routes. Moreover, it has been shown that when resistance has developed after prolonged intramuscular administration, a normal clinical response can again be obtained when the ACTH is given intravenously. This would suggest that the resistance was due to local inactivation of ACTH by the tissues.[25] We have found that prolonged remissions are more likely to occur after the continuous intravenous route than after other methods of administration.

It has been shown, that, at any one time, only a fraction of the administered ACTH is utilized for adrenal cortical stimulation, the remainder being inactivated or destroyed by the body tissues and fluids, including the blood. For this reason, should intravenous ACTH therapy be required simultaneously with a blood transfusion, it should not be added to the blood, but administered separately from a separate container.

In the past 6 months, we have used long-acting ACTH in the form of a gel. These preparations, ACTH-Gel (Armour, 40 I.U. per c.c.) and purified Corticotropin-Gel (Wilson, 100 I.U. per c.c.) have proved not only effective but also most convenient for maintenance therapy, as their use entails only one injection each day or on alternate days.

CORTISONE

At first, cortisone, as a liquid suspension of the acetate, was administered by intramuscular injection, but in September 1950 we commenced to use this suspension by mouth, and now cortisone tablets for oral use is the usual method of administration. With few exceptions, the dosage by either route is essentially the same, but oral cortisone is more efficacious when taken in 3 or 4 divided doses during the 24 hours, because of its greater rate of absorption from the gastro-intestinal tract, whereas intramuscularly, one injection given each day or on alternate days will usually suffice.[26]

For suppresion in the initial stage of the illness, the most effective dosage consists of 300 mg. on the first day, 200 mg. on the second, and 100 mg. thereafter, although in some cases, smaller initial amounts will suffice, whereas in some conditions, notably the collagen diseases, larger amounts may be needed. After optimal clinical response has been obtained, the dose is adjusted for adequate maintenance. As a rule, a reduction to 75 mg. daily suffices, but occasionally larger amounts are needed.

Hydrocortisone, in the free form, is said to exert an effect similar in some respects to that of cortisone, but is equally effective in smaller dosage and is less likely to induce side effects.[27] When injected locally as the acetate, it has been found most useful for the relief of a variety of painful conditions.[28]

As a rule, the most useful guide to adequacy of dosage is the clinical response of the patient, but in cases where the response is not up to expectations the dosage should be reviewed. A slight increase may result in striking improvement. Eosinophil counts may prove of value in deciding whether sufficient adrenocortical stimulation is being obtained with the dosage of ACTH in use, or whether the dose of cortisone is adequate.[29] If a substantial fall in the numbers of circulating eosinophils has not

occurred, an increase in dose is justifiable. Failure to obtain an eosinopenic response with higher dosage of ACTH would indicate either an unresponsive adrenal cortex, due to disease of the adrenal glands or to previous cortisone therapy.

Abrupt cessation of treatment may lead to the withdrawal symptoms of adrenocortical insufficiency with or without an exacerbation of the symptoms of the disease under treatment. This can usually be avoided by a gradual reduction in the daily dose before finally discontinuing the treatment. We have noted that in some conditions manifestations of withdrawal are more likely to occur after a short period of treatment than after the patient has received the hormone for many months.

In evaluating the response to treatment, a distinction is made between general beneficial effects of a non-specific nature and those considered to be related to the disease under treatment. Only the occurrence of the latter is regarded as evidence for the efficacy of the treatment.

The appraisal of the effects of treatment is based on changes in the subjective symptoms, objective clinical manifestations, laboratory findings and X-ray appearances and the degree of improvement is graded according to an arbitrary classification as marked, moderate, slight or nil. The numbers of cases of each disease, the treatment used and the effects of treatment are tabulated in the Tables 2 to 15.

RHEUMATIC AND ARTHRITIC DISEASES

RHEUMATOID ARTHRITIS

Of the 48 patients, 26 were females and 22 males. The ages varied from 25 to 66 years. A satisfactory result was obtained in 43 (89.6%), 20 having derived a marked and 23 a moderate degree of benefit. In one patient in the latter group, a 37-year-old female with evidence of hypothyroidism, cortisone or ACTH in standard dosage failed to bring about significant improvement, even with thyroid medication. When the dosage of either cortisone or ACTH was increased, the arthritis improved but massive oedema ensued and the treatment had to be discontinued. Subsequently, ACTH administered by the 8-hour intravenous infusion method afforded satisfactory relief, but when ACTH-Gel was used for maintenance therapy, this again led to the development of oedema, adequately controlled, however, when the daily ration of potassium chloride was increased to 10 gm.

TABLE 2: RHEUMATIC AND ARTHRITIC DISEASES

Diagnosis	*No. of Cases*	*Treatment*			*Effect of Treatment*				*Deaths*
		A	*C*	*AC*	*Marked*	*Moderate*	*Slight*	*Nil*	
Rheumatoid Arthritis	48	9	24	15	20	23	2	3	2
Ankylosing Spondylitis	9	3	5	1	3	4	1	1	—
Still's Disease ..	1	—	1	—	1	—	—	—	—
Rheumatic Fever	8	5	1	2	5	2	1	—	—
Bacterial Endocarditis ..	2	—	2	—	2	0	—	—	—
Osteoarthritis ..	1	—	1	—	—	—	—	1	—
Osteitis Pubis ..	1	1	—	—	—	—	1	—	—
Totals ..	70	18	34	18					

In the 2 cases in which the effect was considered slight, the disease was in a far-advanced stage with severe long-standing contractures. Of the 3 cases in which no benefit was derived, in 2 the treatment had to be discontinued because of the development of psychotic manifestations. In the remaining case, treated with intramuscular cortisone, no reason for the failure was apparent.

Two patients died during treatment. In one, the cause of death was congestive cardiac failure resulting from aortic incompetence of rheumatic origin and in the other, coronary thrombosis.

In 7 cases, ACTH-Gel was used. In 6 of these this preparation was given for maintenance therapy, after relief had first been obtained by either the intermittent subcutaneous or the intravenous route, and in 1 case the Gel was used from the commencement of therapy.

The continuous method of administration was used in most cases. The duration of treatment varied from 1 to 31 months. Two patients have received continuous treatment for 31 months, one for 28 months, 2 for 22 months, 3 for 21 months, 5 for 19 months, 8 for from 12 to 18 months and the remaining 27 patients for less than 1 year.

A 25-year-old patient with advanced rheumatoid arthritis became pregnant while on cortisone therapy and was delivered uneventfully of a full-term healthy child by caeserean section. There was almost complete freedom from symptoms for 9 weeks before and for 2 weeks after delivery, when an exacerbation occurred, necessitating the resumption of therapy. This patient has since fallen pregnant again.

One patient had psoriasis and another dermatitis herpetiformis, both of which eruptions cleared during therapy. Episcleritis, present in 2 patients, improved. In 4 elderly patients with marked osteoporosis, testosterone or methyl-androstenediol were administered as adjunctive therapy for their anabolic properties.

In 1 patient with a stomal peptic ulcer, a massive gastro-intestinal haemorrhage occurred during cortisone therapy. With blood transfusions the bleeding ceased, despite the continuation of the cortisone therapy. This patient had previously experienced several such haemorrhages and it was considered that a causal relationship did not necessarily exist between the cortisone therapy and the haemorrhage.

In a female patient, a Hunner's ulcer of the urinary bladder improved but later relapsed, despite continuation of the cortisone therapy.

Where a single joint has remained relatively refractory to treatment, periodic intra-articular injections of hydrocortisone acetate have been given into the affected joint. In some of these cases, but not in all, additional temporary relief has thereby been obtained.

Our results indicate that cortisone or ACTH given continuously affords significant and often dramatic relief to a high proportion of patients suffering from rheumatoid arthritis of any grade of severity and that, with few exceptions, untoward effects may readily be prevented or controlled by simple measures, such as salt restriction and a substantial daily ration of potassium chloride. Satisfactory results are reported from other centres,[30] but the same optimism as regards long-term therapy is not shared by all observers.[31]

Ankylosing Spondylitis

Of the 9 patients with ankylosing spondylitis, 8 were males and 1 was a female. Two were brother and sister. The disease was considered to be in an early stage of development in 4 patients and of these, the degree of improvement was marked in 3 and moderate in 1 (a female aged 29 years) who received at different times, cortisone, ACTH and ACTH-Gel. In the latter case the treatment was eventually abandoned because of the occurrence of intractable oedema and pronounced rounding of the facies despite salt restriction and the liberal use of potassium chloride. A satisfactory response was subsequently obtained with deep X-ray irradiation. Although the menses were at times irregular, this patient nevertheless fell pregnant while receiving cortisone.

The disease was in an advanced stage in the remaining 5 patients and of these, improvement was of moderate degree in 3, of slight degree in 1 and absent in the remaining case.

Sufficient time has not yet elapsed to ascertain whether continuous therapy instituted in the early stage of the disease will be effective in preventing the development of ankylosis.

Still's Disease

A dramatic response was obtained with a single 30-day course of cortisone in a 7-year-old boy with a 4-months' history of fever, skin rash, painful swollen joints and lymphadenopathy. No recurrence has occurred during the 24 months which have elapsed since the cortisone therapy was discontinued. Comprehensive investigations were carried out in the course of treatment, the results of which will form the subject of a separate communication.[32]

Rheumatic Fever

Of the 8 patients treated, in 4 this was the primary attack, in 3 a recurrent attack, and in 1 patient the disease was of the chronic active form. Of those in their primary attack, 3 showed a marked response, 2 receiving ACTH alone and 1 ACTH followed by cortisone. One patient treated with ACTH was considered to have obtained only slight relief. Of the 3 patients with recurrent attacks, all treated with ACTH, 2 derived marked, and one moderate benefit.

An 18-year-old male, in whom intramuscular ACTH was commenced 14 days after the onset of his illness and who received 1,280 mg. in 30 days, was completely relieved of all his symptoms by the fourth day. A parasternal diastolic murmur, heard initially, later disappeared. There was no return of symptoms following cessation of treatment nor has evidence of valvular damage become apparent after 15 months.

A 14-year-old Chinese boy, who had been ill with rheumatic fever for 3 weeks, received 850 mg. of ACTH by intramuscular injection over a period of 20 days followed by 1,250 mg. of cortisone given orally over a period of 16 days. A satisfactory response was obtained and no evidence was apparent that involvement of the valves had supervened during the course of treatment or in a subsequent period of 22 months.

A 15-year-old male, with a 4-months' history of chronic active rheumatic fever with carditis, unresponsive to salicylates, showed slow improvement of moderate degree with intramuscular cortisone therapy (2,810 mg. in 26 days) but with no change for the better in the cardiac lesions. He suffered a relapse 5 months later, for which intramuscular ACTH was given (2,260 units in 40 days), but with little significant benefit. When the intravenous route was resorted to (120 units in 6 days), moderate improvement was obtained, although a slight recrudescence of symptoms occurred when ACTH therapy was withdrawn.

It would appear from this small series of cases that with the use of ACTH or cortisone, satisfactory control of the manifestations of rheumatic fever and the prevention of valvular disease can only reasonably be anticipated when treatment is instituted early in the primary attack and before gross cardiac lesions have supervened. It is suggestive, too, that ACTH administered by the intravenous route is the method by which a more effective and lasting response may be obtained.

Differences of opinion exist among workers about the efficacy of ACTH and cortisone in the treatment of rheumatic fever, but on the whole it is generally agreed that a worth-while result is obtained in a significant proportion of cases.[33]

Subacute Bacterial Endocarditis

A prompt and favourable response was obtained with cortisone therapy in 2 male patients, aged 42 and 17 years respectively. In both cases the administration of antibiotics in massive dosage had hitherto failed to influence the course of the disease. In both patients gross valvular disease was present, but this apparently remained uninfluenced by the hormone therapy.

In the first case no recurrence has occurred during the 6 months which have elapsed since the discontinuation of cortisone, which had been given for a period of 12 weeks. In the second case, in which positive blood cultures of a non-haemolytic streptococcus were obtained, suppression of the disease has been maintained satisfactorily on a small daily dose of cortisone for a period of 8 weeks. As far as is known, no other instances of this disease, treated with ACTH or cortisone, have so far been reported.

Collagen Diseases

Systemic Lupus Erythematosus

Of the 7 patients, 5 were females and 2 males. There were 2 deaths. The first patient, a gravely ill 33-year-old female, was treated in July 1949 with an early preparation of ACTH (Organon), of which she received 500 sudanophobic units over a period of 20 days. There was distinct improvement with a return of strength and

TABLE 3: COLLAGEN DISEASES

Diagnosis	*No. of Cases*	*Treatment*			*Effect of Treatment*				*Deaths*
		A	*C*	*AC*	*Marked*	*Moderate*	*Slight*	*Nil*	
Systemic Lupus Erythematosus	7	2	1	4	3	3	1	—	2
Discoid Lupus Erythematosus	1	—	1	—	—	—	—	1	—
Periarteritis Nodosa	3	2	—	1	1	—	—	2	2
Dermatomyositis	3	2	—	1	1	1	—	1	1
Scleroderma	9	2	4	3	2	1	2	4	—
Totals	23	8	6	9					

appetite, an increase in the sense of well-being, disappearance of the haemorrhagic manifestations and partial healing of the lesions of the lips, mouth, vagina and eyes. Within a few days of stopping the ACTH (owing to lack of supplies), the condition relapsed and she continued to deteriorate steadily, with recurring convulsive seizures, until her death 6 months later.

In the other fatal case, a female aged 22 years, the symptoms of the disease had been well controlled for 10 months on ACTH followed by cortisone, after which renal failure and hypertension rapidly supervened, followed by death within 1 month.

With continuous cortisone therapy, the disease has been adequately suppressed in 2 patients. In 1 of these, a 17-year-old Indian girl, who has received ACTH or cortisone continuously for 28 months, the omission of even a single oral dose of cortisone prescribed to be taken at 6-hourly intervals, is followed within a few hours by a recrudescence of joint pains and a rise in temperature. On each occasion, resumption of the prescribed regime affords prompt relief.

The other patient, a female aged 35 years, while receiving cortisone suffered from a cerebral episode characterized by coma of 2 days' duration, followed by hemiplegia and aphasia which cleared completely after 7 days, although cortisone therapy was continued. Despite the presence of renal involvement, this patient continues to remain free of symptoms and shows no evidence of deterioration of kidney function after 1 year of continuous cortisone therapy.

A male patient 43 years of age, with marked renal disease, continues to derive moderate benefit from ACTH or cortisone given for a period of one year, although nitrogen retention has recently become evident.

It is clear that relief of symptoms, often dramatic, and occasionally life-saving, may be obtained with the use of ACTH or cortisone, but it is not yet apparent whether the average survival time of the disease can be prolonged by continuous therapy carried out indefinitely. The impression has been gained that for the purpose of maintenance therapy the disease process is more adequately and readily suppressed with the use of oral cortisone than of ACTH. The chief complicating factor precluding successful maintenance therapy with these agents appears to be that of progressive renal failure. Several reports concerning the use of ACTH and cortisone in this disease have appeared.[34]

PERIARTERITIS NODOSA

In the 2 fatal cases the patients received ACTH for only 24 hours on the day before death. At autopsy the diagnosis was confirmed. The third case was that of a 13-year-old girl in whom a satisfactory remission has been maintained with ACTH and ACTH-Gel for 9 months without apparent deterioration in her condition. Varying degrees of success with the use of these hormones for periarteritis nodosa have been reported.[35]

DERMATOMYOSITIS

The first case was that of a 42-year-old male, gravely ill with advanced acute dermatomyositis, complicated by dysphagia and respiratory embarrassment. The administration of an early preparation of ACTH (Organon) in the daily dosage of 30 sudanophobic units for 4 days failed to prevent a fatal outcome.

The second case, the details of which have been published elsewhere,[36] was that of a 35-year-old male suffering from dermatomyositis of extreme severity, who made a dramatic recovery following the use of ACTH and who has remained in good health for 27 months following the termination of therapy.

The third patient, a 72-year-old male with the chronic form of the disease, has required continuous cortisone therapy for a period of 22 months in order to maintain a moderate degree of relief. Cessation of treatment is invariably followed by a prompt exacerbation of symptoms. Several reports of ACTH and cortisone therapy for this disease have appeared, but the results are not uniformly satisfactory.[37]

SCLERODERMA

Four of the 9 patients with scleroderma had co-existing Raynaud's disease, and of these only 1, an early case, derived significant benefit from ACTH and cortisone therapy, but in respect only of the sclerodermatous process.

Of the 5 patients without the peripheral vasomotor disturbance, 4 showed a marked degree of improvement and 1 patient, in the advanced stage of the disease, was considered to have derived moderate benefit. Discontinuation of therapy was invariably followed by a prompt return of symptoms. Sufficient time has not yet elapsed to judge whether this form of therapy, instituted in the early stages of the disease and thereafter continued indefinitely, will succeed in preventing the progression of the sclerodermatous process. That this may be the case is suggested by the observations on patients maintained on therapy for periods of several months. The detailed results, with those of additional cases, will be reported separately.[58] Reports of satisfactory therapeutic responses have been published.[59]

PULMONARY DISEASES

BRONCHIAL ASTHMA

Of the 31 patients, 28 (90%) derived significant benefit.

Five received *a single* course of ACTH or cortisone, and of these, 1 was markedly improved. Two showed moderate improvement, but 1 of these subsequently died of uraemia and cardiac failure due to cor pulmonale resulting from emphysema. The treatment was abandoned in one case because of a lack of response. In another case, the patient, a 54-year-old male on the third day of

TABLE 4: PULMONARY DISEASES

Diagnosis	No. of Cases	Treatment			Effect of Treatment				Deaths
		A	C	AC	Marked	Moderate	Slight	Nil	
Bronchial Asthma	31	9	13	9	19	9	2	1	4
Chronic Emphysema and Cor Pulmonale	3	1	2	—	—	—	—	3	1
Pneumonia	3	3	—	—	2	—	1	—	—
Pulmonary Embolism	4	4	—	—	3	1	—	—	—
Irritant Gas Poisoning	1	1	—	—	1	—	—	—	—
Totals	42	18	15	9					

the course of cortisone therapy, died suddenly in acute respiratory failure a few minutes after having received an intramuscular injection of 100 mg. of cortisone. Permission for autopsy was not granted and the cause of death was not established.

In 9 patients, remissions of varying duration occurred, but because of relapses, *repeated* courses of treatment were needed. In one patient of this group, an occasional injection of ACTH-Gel, self-administered, has sufficed to give sufficient relief for a restful night. Intermittent treatment has been carried out for 24 months in 2 patients, for 20 months in 2, and for 12 months or less in 5.

Seventeen patients, all with chronic intractable asthma, have required *continuous* therapy. This has been carried out for 18 months in 2 patients, for 12 months in 2, for from 8 to 10 months in 6, and for 6 months or less in the remaining 7 patients.

Status asthmaticus was present in several patients and in each instance was readily brought under control. In most of the cases in which both ACTH and cortisone have been used at different times, each form of medication has proved equally efficacious, but in a few instances the one agent was found to be effective after no response had been obtained with the other.

On occasions it has transpired that ACTH given by continuous intravenous infusion has proved effective when no benefit had been derived by the intermittent intramuscular or subcutaneous route of administration.

When emphysema of severe degree was present as a complicating factor in asthmatic patients, the response to this form of therapy is found to be less satisfactory and in 2 instances this condition indirectly was the cause of death.

In 14 cases the improvement in pulmonary ventilation during the course of treatment was assessed by serial determinations of the maximum breathing capacity and vital capacity.

Satisfactory control of asthma with ACTH and cortisone has been reported by several observers.[41]

Chronic Emphysema with Cor Pulmonale

Even when a significant degree of bronchospasm was present in patients with chronic cor pulmonale resulting from emphysema, no significant benefit was derived from this form of therapy.

Pneumonia

In 2 patients gravely ill with pneumonia and receiving antibiotic therapy, the use of ACTH was considered to have aided recovery. In the third case, the degree of benefit so derived was considered to have been slight. The use of these agents as adjunctive therapy in pneumonia and other acute infections has been well documented.[41]

Pulmonary Embolism

Three patients, who continued to suffer from the effects of acute pulmonary embolism and severe shock despite the use of anti-coagulant therapy, were treated with ACTH by continuous intravenous infusion while continuing with heparinization. Prompt and dramatic improvement ensued. Not only was the state of shock promptly controlled but the rate of resolution of the infarcted lung, as well as that of the deep crural vein thrombosis, appeared thereby to have been hastened. The duration of ACTH treatment in the first patient was 1 day and in the second patient 4 days. The third patient, severely collapsed and gravely ill, received intravenous ACTH for 15 days with an excellent response, but owing to a recurrence of pulmonary embolism 4 days later, ACTH treatment was again instituted with a dramatic effect, and continued for 7 days. In a fourth case, a patient with rheumatic valvular heart disease, the benefit derived from ACTH therapy for 10 days in respect of the pulmonary embolization was considered to have been only moderate in degree.

Irritant Gas Poisoning

A 33-year-old male, after exposure to nitric oxide fumes, was gravely ill with advanced pulmonary oedema and congestive cardiac failure. As he had failed to respond to various forms of treatment and while in a semi-moribund state, ACTH therapy was instituted and continued for 1 week. This resulted in a prompt and dramatic recovery followed by gradual improvement. This treatment is considered to have been life-saving, although 5 months later evidence of reduced pulmonary ventilation had become apparent, as judged by determinations of the vital capacity and maximum breathing capacity.[42]

LIVER DISEASES

Infective Hepatitis

Of the 6 patients with infective hepatitis, 2 died. The first fatal case was that of a 33-year-old female in advanced post-hepatitic cholaemia with ascites and oedema, to whom ACTH was administered intramuscularly for only 3 days before her death. The second fatal case was that of a 35-year-old male in deep cholaemic coma, who received intravenous ACTH for 3 weeks, followed by oral cortisone for 6 days. Consciousness was fully regained within 3 days and the jaundice lessened. A massive gastro-intestinal haemorrhage occurred on the twenty-seventh day of treatment and proved rapidly fatal. Autopsy revealed the presence of liver cirrhosis with acute hepatitis of recent origin and rupture of an oesophageal varix.

TABLE 5: LIVER DISEASES

Diagnosis	*No of Cases*	*Treatment*			*Effect of Treatment*				*Deaths*
		A	*C*	*AC*	*Marked*	*Moderate*	*Slight*	*Nil*	
Infective Hepatitis ..	6	5	—	1	3	1	—	2	2
Cirrhosis with Jaundice ..	3	2	—	1	—	2	—	1	—
Hepato-Renal Syndrome ..	1	1	—	—	—	—	—	1	1
Total ..	10	8	—	2					

In one patient, intravenous ACTH treatment was instituted but was discontinued on the seventh day because of perforation of a duodenal ulcer. Recovery was uneventful following surgical intervention.

Three patients were considered to have derived distinct benefit from ACTH therapy, administered by the intravenous route. The first case was that of a 26-year-old male who, commencing on the twelfth day of the disease, received intravenous ACTH therapy for 16 days. By the fourth day, jaundice was no longer apparent and the liver

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and spleen could not be felt. The serum bilirubin had reached normal levels on the twelfth day of treatment. After 3 weeks of bed rest, he was discharged, but 2 weeks later there was a recrudescence of the jaundice, which responded promptly with the re-institution of intravenous ACTH treatment, carried out for a further 13 days.

The second case was that of a 24-year-old female, in the fourth month of pregnancy, who suddenly became gravely ill with intense jaundice and stupor. Hysterotomy was performed under local anaesthesia, following which severe circulatory collapse supervened with marked abdominal distension due to paralytic ileus. The jaundice and stupor deepened and her condition appeared hopeless. ACTH therapy was commenced immediately, by continuous intravenous infusion, in the daily dosage, of 30 mg. for 5 days and 5 mg. for 2 more days. By the second day the stupor had lessened and the intensity of the jaundice had visibly diminished, the serum bilirubin being 12.5 mg. per 100 c.c., a pre-treatment level not having been obtained for comparison. With the aid of continuous gastro-intestinal drainage the paralytic ileus was relieved and the abdominal distension subsided. The serum bilirubin level fell to 3.9 mg. on the fifth day and to 1.4 mg. per 100 c.c. 3 days later, by which time there was no visible icterus and it was apparent that the patient had made a dramatic and rapid recovery.

The third case was that of a 19-year-old male who, in the eleventh week after the onset of the disease, was still intensely jaundiced (serum bilirubin 40 mg. per 100 c.c.) and was showing evidence of severe liver damage and commencing cholaemia. Following the institution of ACTH therapy, there was a prompt and rapid decrease in the intensity of the jaundice and dramatic clinical improvement. The infusions of ACTH were administered daily for a period of 14 days, by which time the serum bilirubin had fallen to 5 mg. per 100 c.c. Thereafter infusions were given on alternate days for 3 weeks and, at intervals of 3 or 4 days, for a further 2 weeks, during which time the serum bilirubin remained throughout at normal levels. Two months after the cessation of treatment the patient was found to be clinically well, having gained 36 lb. in weight and all the previously deranged tests for liver function had returned to normal, with the exception of the level of serum cholinesterase, which was still decreased to 50% of normal. ACTH therapy, by the intravenous route in particular, has been reported to have proved significantly beneficial in several instances of acute viral hepatitis and of homologous serum jaundice.[43]

CIRRHOSIS WITH JAUNDICE

In 2 cases, in which ACTH therapy was used, there was temporary decrease in the degree of jaundice but without significant improvement in liver function tests. Relapses ensued shortly after the end of each course of treatment.

A 33-year-old jaundiced male with a history of bouts of jaundice since childhood, in whom a liver biopsy revealed a mild degree of cirrhosis and who exhibited mild symptoms of a psychopathic personality, failed to derive any significant benefit from ACTH therapy administered for 3 weeks. The treatment was discontinued because of an intensification of the disordered mental state.

A 15-year-old girl presented with jaundice of 6 weeks' duration and enlargement of the liver and spleen. Liver biopsy revealed cirrhosis. Eight years before a similar clinical condition had been present. Intravenous ACTH therapy was given each day for 16 days, on alternate days for 10 days and on every third day for a further 18 days. The serum bilirubin fell to within normal limits within a week, but other tests indicating deranged liver function showed no material change, with the exception of a decrease in serum globulin. A second biopsy revealed no alteration in the histological appearance of the liver. Two months after the ACTH therapy had been discontinued, the jaundice reappeared. Cortisone therapy again led to a decrease in the serum bilirubin, but as no material benefit was considered to have resulted as regards the cirrhosis, the steroid therapy was discontinued. Cirrhosis with jaundice has been reported to have reacted favourably to ACTH therapy.[44]

NEURO-PSYCHIATRIC DISEASES

DELIRIUM TREMENS

In each of the 3 patients with delirium tremens, a prompt recovery was obtained within 24 hours of instituting intramuscular ACTH therapy continued for a week. These findings are in accord with those of other writers.[45]

TABLE 6: NEURO-PSYCHIATRIC DISEASES

Diagnosis	*No. of Cases*	*Treatment*			*Effect of Treatment*				
		A	*C*	*AC*	*Marked*	*Moderate*	*Slight*	*Nil*	*Deaths*
Delirium Tremens	3	3	—	—	3	—	—	—	—
Alcoholic Peripheral Neuritis	1	1	—	—	1	—	—	—	—
Korsakoff's Psychosis	3	2	—	1	—	1	—	2	—
Sydenham's Chorea	1	—	—	1	1	—	—	—	—
Disseminated Sclerosis ..	3	2	1	—	1	1	1	—	—
Myasthenia Gravis	1	—	1	—	—	—	—	1	1
Parkinson's Disease	2	1	1	—	—	1	—	1	—
Chronic Adhesive Arachnoiditis ..	1	—	1	—	1	—	—	—	—
Phantom Limb Causalgia ..	1	—	1	—	—	—	—	1	—
Chronic Tension Headaches ..	2	—	2	—	—	—	—	2	—
Sciatic Syndrome	3	2	1	—	1	—	—	2	—
Totals ..	21	11	8	2					

ALCOHOLIC PERIPHERAL NEUROPATHY

A 45-year-old man with severe alcoholic peripheral neuritis improved rapidly when treated with subcutaneous ACTH together with vitamins and a high protein diet for a period of one month, whereas on a previous admission with peripheral neuritis of a lesser degree of severity, several months elapsed before significant improvement occurred with the use only of conventional vitamin and dietetic therapy.

KORSAKOFF'S PSYCHOSIS

Of three cases of Korsakoff's psychosis, a moderate degree of improvement was considered to have resulted from the use of ACTH in one patient, whereas in the others no benefit was derived from either ACTH or cortisone.

SYDENHAM'S CHOREA

A 15-year-old female with severe generalized chorea, after having shown marked improvement with ACTH therapy given for 7 weeks, relapsed after several months, but again responded satisfactorily when treated with oral cortisone.

DISSEMINATED SCLEROSIS

A 45-year-old male with a useless left upper limb due to weakness, paraesthesia and marked astereognosis, rapidly regained the use of the limb when treated with intravenous ACTH for 3 weeks. The improvement has been maintained for a period of 3 months following the cessation of treatment.

A 38-year-old female, who had experienced periodic neurological disturbances for a period of 17 years, presented with a moderately severe ataxic paraplegia which had persisted without abatement for 6 months. Intravenous ACTH for 10 days and in the form of the Gel for 27 days, resulted in partial but significant improvement in gait. After cessation of treatment the disability returned, but to a degree of severity less than that present before the institution of hormonal therapy.

In the third case, a patient with advanced spastic ataxic paralysis, no benefit was derived from ACTH-Gel therapy, but slight improvement seemed to have occurred with oral cortisone. Significant improvement with these hormonal agents in a proportion of cases has been reported by other writers.[46]

CHRONIC ADHESIVE ARACHNOIDITIS

Prompt and dramatic improvement took place with oral cortisone in a 60-year-old male suffering from progressive spastic quadriplegia of 20 years' duration proved by myelography to be due to chronic adhesive arachnoiditis. Whereas formerly he suffered severe radicular pains and the difficulty in walking was such that he could barely get about even with the aid of sticks, with cortisone therapy he has been relieved completely of the severe pains and he has been able to walk with greater ease, due, in part, to marked lessening of spasticity. After 6 months of continuous therapy, the improvement has been maintained.

The beneficial effect obtained in this case is suggestive of continued activity of the arachnoiditic lesion and indicates the persistence of its irritant nature, despite the long duration of the disease.

To my knowledge, the use of cortisone in the treatment of this neurological disorder has not been reported before.

ENDOCRINE DISEASES

ADDISON'S DISEASE

A 33-year-old male has been satisfactorily maintained for 31 months on an average daily dose of 12.5 mg. of oral cortisone supplemented by 1 mg. of sublingual desoxycorticosterone.

The disturbance in water metabolism, as judged by the Robinson-Power-Kepler test, was restored to normal only when cortisone was included in the regimen.

In a 46-year-old male suffering from a severe Addisonian crisis, the use for 2 days of intramuscular cortisone in high dosage in conjunction with other conventional forms of therapy, failed to prevent a fatal outcome. The additional benefit derived from cortisone in the maintenance therapy of Addison's disease is well documented.[47]

TABLE 7: ENDOCRINE DISEASES

Diagnosis	*No. of Cases*	*Treatment*			*Effect of Treatment*				*Deaths*
		A	*C*	*AC*	*Marked*	*Moderate*	*Slight*	*Nil*	
Addison's Disease	2	—	2	—	1	—	—	1	1
Hypopituitarism	2	—	2	—	2	—	—	—	—
Thyrotropic Ophthalmopathy ..	1	—	1	—	—	—	—	1	—
Totals ..	5	—	5	—					

HYPOPITUITARISM

In conjunction with desiccated thyroid and desoxycorticosterone, the use of cortisone in an average daily dose of 25 mg. has controlled the severe symptoms of hypopituitarism adequately for 12 months in a 72-year-old man with a chromophobe adenoma of the pituitary and for 8 months in a 46-year-old woman with Sheehan's syndrome. The value of these hormones in pituitary insufficiency has been amply confirmed.[48]

METABOLIC DISORDERS

ACUTE GOUTY ARTHRITIS

All 9 patients with acute gouty arthritis derived some benefit from both ACTH and cortisone, but with the latter medication (4 cases), relapse invariably followed cessation of treatment, whereas when a course of ACTH treatment was given by the daily 8-hour intravenous infusion method for a period of from 10 to 14 days (3 cases), the therapeutic effect was dramatic and the remissions so induced have so far persisted for many months. The effects on acute gout of intramuscular ACTH and of cortisone given for short periods have been reported.[49]

TABLE 8: METABOLIC DISEASES

Diagnosis	*No. of Cases*	*Treatment*			*Effect of Treatment*				*Deaths*
		A	*C*	*A C*	*Marked*	*Moderate*	*Slight*	*Nil*	
Gouty Arthritis	9	3	4	2	4	5	—	—	—
Alkaptonuric Arthritis	1	—	—	1	—	1	—	—	—
Generalized Myositis Ossificans	1	1	—	—	—	—	—	1	—
Acute Acquired Porphyria ..	2	2	—	—	—	—	—	2	1
Totals ..	13	6	4	3					

ALKAPTONURIC (OCHRONOTIC) ARTHRITIS

This case, a description of which has been published,[50] was that of a 67-year-old man with extensive spondylitis and severe arthritis involving the larger joints. He obtained significant relief when treated with subcutaneous ACTH for 8 weeks followed by oral cortisone for 3 months. The ochronosis and alkaptonuria were uninfluenced by this therapy.

GENERALIZED MYOSITIS OSSIFICANS

No benefit was derived from ACTH administered daily by the 8-hour intravenous infusion method for 5 weeks to a 17-year-old girl with extensive generalized myositis ossificans of 10 years' duration. Biopsies obtained before and at the termination of treatment revealed no change in the histological appearance of the diseased muscle.

ACUTE ACQUIRED PORPHYRIA

In 2 female patients aged 44 and 32 years respectively, with attacks of acute acquired porphyria, the use of intravenous ACTH therapy given for a week failed to bring about any significant improvement in the one, or to prevent a fatal outcome from respiratory paralysis in the other.

EYE DISEASES

Of this small group of 7 cases, the effects obtained in 3 are worthy of special mention. The first case, a 53-year-old man with blurring of vision of the right eye of 6 weeks' duration, was found to have bilateral chorio-retinitis with involvement of the macula in the right eye. Perimetry revealed bilateral scotoma, and the visual acuity was 6/36 to 6/24 on the right and 6/9 on the left. With ACTH-Gel therapy, 620 I.U. in a period of 3 weeks, the visual acuity increased to 6/18, but the blurring remained unchanged. When oral cortisone therapy was instituted, rapid improvement took place. Within a month, the visual acuity had increased to 6/6 and the blurred vision had disappeared. The improvement has been maintained for 3 months following cessation of therapy, but the retinal appearances remain unchanged.

TABLE 9: EYE DISEASES

Diagnosis	*No. of Cases*	*Treatment*			*Effect of Treatment*				*Deaths*
		A	*C*	*AC*	*Marked*	*Moderate*	*Slight*	*Nil*	
Keratitic Ulceration	1	1	—	—	1	—	—	—	—
Pemphigus Oculi	1	—	1	—	—	—	—	1	—
Chronic Iridocyclitis	2	—	2	—	—	—	1	1	—
Choroiditis	1	—	—	1	1	—	—	—	—
Macular Degeneration	1	—	1	—	—	1	—	—	—
Hypertensive Neuroretinitis	1	—	1	—	—	1	—	—	—
Totals	7	1	5	1					

The second case was that of a 31-year-old woman with the complaint of impairment of central vision in the left eye for 5 years and in the right for 3 months. This was found to be due to macular degeneration of undetermined origin. After 3 subconjunctival implantations of cortisone suspension followed by continuous intramuscular and oral cortisone therapy for a period of 6 months, the visual acuity had improved from 6/60 to 6/18 and the extent of the paracentral scotomata was found to have diminished.

The third case was that of a 61-year-old man suffering from malignant hypertension with paroxysmal left ventricular failure, severe headaches and gross papilloedema with such failing vision that he could neither read nor recognize faces. Following thoraco-dorsal lumbar sympathectomy and splanchnicectomy, the cardiac status improved, the average blood pressure levels decreased, headaches were relieved, but the vision remained unchanged. Five weeks after the operation, oral cortisone therapy was instituted in the dosage of 300 and 200 mg. on successive days followed by 100 mg. daily. Within 2 days his vision had commenced to improve and after 2 weeks he was able to recognize faces and read the headlines of papers. After 18 days he discontinued the treatment of his own accord and no further improvement took place. One month later, cortisone therapy was resumed and within a week his vision had improved to the extent that he was able to read small newsprint. Cortisone was continued for 9 weeks and the improvement in vision has been maintained for 3 months since the discontinuation of therapy. On funduscopic examination, no evidence of papilloedema could be detected. Improvement in vision with the use of ACTH in a patient with hypertensive papilloedema has been reported.[51] The beneficial effects of ACTH and cortisone therapy in a wide variety of eye diseases has been documented extensively.[52]

SKIN DISEASES

In a case of drug eruption due to Epanutin (Dilantin), intramuscular ACTH promptly relieved the itching and the eruption cleared completely in 5 days and did not recur after cessation of treatment. A patient with mercurial dermatitis obtained complete relief with oral cortisone given for 8 weeks. A 36-year-old female with scleredema adultorum (Buschke's disease) failed to improve with intravenous ACTH therapy given daily for a period of 15 days. In the remaining conditions listed, the skin lesions were more or less controlled by ACTH or cortisone but tended to reappear when treatment was discontinued.

An extensive literature has appeared describing the therapeutic effects of ACTH and cortisone in a wide variety of skin diseases.[53]

TABLE 10: SKIN DISEASES

Diagnosis	*No. of Cases*	*Treatment*			*Effect of Treatment*				*Deaths*
		A	*C*	*AC*	*Marked*	*Moderate*	*Slight*	*Nil*	
Drug Eruption	2	1	1	—	2	—	—	—	—
Psoriasis	2	—	1	1	2	—	—	—	—
Pemphigus Vulgaris	1	—	—	1	1	—	—	—	—
Herpetic Stomato-Vaginitis	1	—	—	1	1	—	—	—	—
Beschet's Syndrome	1	—	—	1	—	1	—	—	—
Exfoliative Dermatitis	1	1	—	—	—	1	—	—	—
Scleredema Adultorum	1	1	—	—	—	—	—	1	—
Totals	9	3	2	4					

PERIPHERAL VASCULAR DISEASES

As a result of acute ilio-femoral artery thrombosis in a 55-year-old female, the foot showed incipient gangrene and the entire limb was pale and cold with anaesthesia present to the level of mid-thigh. After no significant improvement had occurred on continuous heparinization for 2 days, ACTH was added to the intravenous infusion

TABLE II: PERIPHERAL VASCULAR DISEASES

Diagnosis	No. of Cases	Treatment			Effect of Treatment				Deaths
		A	C	AC	Marked	Moderate	Slight	Nil	
Acute Femoral Artery Thrombosis with Gangrene	1	1	—	—	—	1	—	—	—
Generalized Thrombophlebitis with Cerebral Involvement	1	1	—	—	—	—	—	1	1
Thromboangeitis Obliterans with Ulceration	1	1	—	—	—	—	—	1	—
Totals	3	3	—	—					

and continued for 3 days. Within the first 24 hours a definite change was observed in that the extent of the anaesthesia and the ischaemia diminished to the level of the lower third of the leg and the severe pain was largely relieved.

Further improvement occurred during the next few days with the result that the limb was eventually salvaged, the residual lesion consisting of gangrene confined to the heel and toes. The part played by ACTH in this case remains uncertain, but further experience is needed concerning the possible value of ACTH in diminishing the extent of infarcted tissue and in relieving the pain of acute arterial occlusion.

Although evidence has been put forward that the use of ACTH and cortisone promotes intravascular clotting, it is maintained by others that this effect occurs on withdrawing these hormones rather than during their administration.[54]

BLOOD DISEASES

Idiopathic Thrombocytopenic Purpura

The successfully treated case was that of a 42-year-old male with purpura of 6 months' duration. The haematological features included prolonged bleeding time, low platelet count, increased capillary fragility, paucity of megakaryocytes, normal prothrombin time, diminished prothrombin consumption and normal antithrombin content. ACTH administered intravenously for 17 days induced a remission in which the numbers of megakaryocytes returned to normal; 38 days after stopping treatment the condition commenced to relapse, but the numbers of megakaryocytes had not diminished. Oral cortisone promptly brought about a remission, which was maintained until this agent was withdrawn 46 days later, when a relapse again occurred. With re-institution of cortisone therapy the bleeding ceased, but returned promptly when treatment was discontinued 100 days later. Subsequently, with the continuous use of cortisone, the disease has been controlled adequately.

On the other hand, two 17-year-old female patients with idiopathic thrombocytopenic purpura failed to improve when treated for 10 and 8 weeks respectively with ACTH followed by cortisone. Subsequently, in both patients, a prompt and favourable response was obtained with splenectomy. Several reports of the successful use of ACTH and cortisone in purpura have appeared.[55]

TABLE 12: BLOOD DISEASES

Diagnosis	No. of Cases	Treatment			Effect of Treatment				Deaths
		A	C	AC	Marked	Moderate	Slight	Nil	
Thrombopenic Purpura	3	—	—	3	1	—	—	2	—
Agranulocytosis	1	1	—	—	—	—	—	1	1
Aplastic Anaemia	2	—	1	1	—	—	—	2	—
Totals	6	1	1	4					

Agranulocytosis

A 58-year-old male with agranulocytosis resulting from overdosage with a nitrogen mustard derivative (R 48), received intravenous ACTH for 8 days, but failed to show any response and died of uraemia. In several instances, a favourable response in this blood dyscrasia has been attributed to ACTH or cortisone.[56]

Aplastic Anaemia

The anaemia of primary erythrocytic aplasia of the bone marrow in a 51-year-old woman failed to respond to ACTH administered by the intramuscular and intravenous routes, given for 25 days, or to oral cortisone given in 2 courses of 25 days and 3 months respectively. A 68-year-old female with myelofibrotic aplastic anaemia showed no haematological improvement when given cortisone orally for 4 weeks. Reports of the favourable influence of these agents in a few cases of refractory anaemia have appeared.[57]

LEUKAEMIAS

Two patients with acute lymphoblastic leukaemia, both children, one treated with ACTH and cortisone and the other with cortisone only, improved in respect of the peripheral blood picture and of the size of the spleen, liver and lymph nodes, but failed to maintain the improvement. Six patients with leukaemia (2 acute lymphoblastic, 2 acute myeloblastic, 1 subacute monocytic and 1 chronic monocytic) failed to improve in any respect other than a temporary increase in the sense of well-being. On the other hand, 2 patients with chronic lymphatic leukamia appeared to have derived distinct benefit, as regards the blood picture and the enlarged spleen and lymph nodes, with the use of intravenous ACTH followed by continuous oral cortisone therapy for 6 and 3 months respectively.

TABLE 13: LEUKAEMIAS

Diagnosis	No. of Cases	Treatment			Effect of Treatment				Deaths
		A	C	AC	Marked	Moderate	Slight	Nil	
Acute Lymphoblastic	4	1	2	1	—	2	—	2	4
Acute Myeloblastic	2	1	1	—	—	—	—	2	2
Subacute Monocytic	1	—	1	—	—	—	—	1	1
Chronic Monocytic	1	—	—	1	—	—	—	1	—
Chronic Lymphatic	2	2	—	—	2	—	—	—	—
Totals	10	4	4	2					

An extensive literature has appeared concerning the use of these hormones in the treatment of leukaemia.[58] It appears that in a proportion of cases of acute leukaemia, temporary improvement may be obtained, whereas in the chronic form only those of the lymphatic type can be expected to derive significant benefit.

NEOPLASTIC DISEASES

LYMPHOSARCOMA

In a 50-year-old male presenting with a gastric ulcer, exploratory laporotomy revealed a sarcoma of the stomach with lymph node involvement, for which gastrectomy was performed. Shortly afterwards generalized lymph node enlargement became evident, proved by biopsy to be due to lymphosarcoma. With intravenous ACTH therapy, the enlarged lymph glands rapidly regressed but reappeared

TABLE 14: NEOPLASTIC DISEASES

Diagnosis	*No. of Cases*	*Treatment*			*Effect of Treatment*				*Deaths*
		A	*C*	*AC*	*Marked*	*Moderate*	*Slight*	*Nil*	
Lymphosarcoma	1	—	—	1	1	—	—	—	—
Reticulum Cell Sarcoma	1	1	—	—	—	—	—	1	1
Hodgkin's Disease	2	1	1	—	—	—	—	2	2
Myelomatosis	4	—	4	—	—	—	—	4	1
Angiosarcomatosis	1	—	—	1	—	—	—	1	1
Pharyngeal Carcinoma	1	1	—	—	—	1	—	—	1
Metastatic Carcinoma	6	3	1	2	—	1	1	4	5
Totals	16	6	6	4					

4 weeks after having discontinued ACTH treatment. With oral cortisone therapy regression of the lymphadenopathy again rapidly occurred and a remission has so far been maintained with cortisone for 6 months.

A 55-year-old patient with a pharyngeal carcinoma, for which deep X-ray irradiation had previously been given, was considered to have derived distinct benefit from ACTH therapy given intermittently for 16 months, in that intractable pain and dysphagia were markedly relieved. Death was due to pulmonary embolism arising from deep crural vein thrombosis.

METASTATIC CANCER

Six patients with metastatic cancer received hormonal treatment and of these only 2 were considered to have derived some degree of benefit.

A 60-year-old male with a cerebral metastasis arising from a bronchial carcinoma showed distinct, though slight, improvement in respect of hemiparesis, vertigo and headache, although more pronounced improvement later ensued with the application of deep X-ray irradiation. Despite continued ACTH and cortisone therapy, bony metastases developed with progressive deterioration before death.

The second case was that of a 60-year-old female, gravely ill and severely disabled with rapidly progressing lymphangitic carcinomatosis of the lungs arising 2 years after amputation of a breast for cancer. Androgen therapy led to a violent exacerbation of her symptoms and was discontinued after 2 days. ACTH therapy was then instituted, but caused a similar deterioration in her condition. With oral cortisone therapy she promptly improved in that the symptoms of intractable cough, severe pains, marked breathlessness and the sensation of tightness of the chest were markedly relieved, unaccompanied, however, by any change in the X-ray appearances of the lungs. In the course of 6 months' of continuous oral cortisone therapy in the daily dosage of 100 mg., the rate of deterioration is considered to have been significantly retarded. The adjunctive use of deep X-ray irradiation for a short period and of aminopterin and triethylene melamine did not appear to have afforded additional benefit.

The improvement with cortisone in this case can probably be explained on the basis of a reduction in the inflammatory reaction induced by the cancerous infiltration, although, in view of the deleterious effect noted with the administration of testosterone and ACTH, it remains a matter for conjecture whether the cortisone exerted a retarding action on the neoplastic growth through the mechanism of adrenocortical suppression.

In the remaining 4 cases, no significant benefit was obtained, other than that afforded by a temporary increase in the sense of well-being.

Despite the limited value of ACTH and cortisone in the treatment of neoplastic diseases, an extensive literature has nevertheless appeared, with particular stress on adrenocorticoid metabolism in malignant disease.[59]

MISCELLANEOUS CONDITIONS

SARCOIDOSIS

A 34-year-old male presented with a syndrome comprising bouts of fever with polyarthritis, bilateral hilar adenopathy and subcutaneous nodules, proved histologically to be due to sarcoidosis. He improved significantly when ACTH-Gel was administered for a period of 38 days, although

TABLE 15: MISCELLANEOUS CONDITIONS

Diagnosis	*No. of Cases*	*Treatment*			*Effect of Treatment*				*Deaths*
		A	*C*	*AC*	*Marked*	*Moderate*	*Slight*	*Nil*	
Sarcoidosis	2		—	2	1	1	—	—	—
Ulcerative Colitis with Arthritis	1	—	—	1	—	1	—	—	—
Cardiac Arrhythmia	2	—	2	—	—	1	—	1	—
Idiopathic Bowel and Bladder Ileus	1	1	—	—	—	—	—	1	—
Surgical Shock	2	2	—	—	—	1	—	1	2
Acute Pancreatitis	2	2	—	—	1	1	—	—	—
Caustic Soda Poisoning	2	1	—	1	1	1	—	—	—
Totals	12	6	2	4					

the pulmonary lesion did not regress until the ACTH had been given by the intravenous method for 7 days. Satisfactory control of the symptoms was subsequently maintained with continuous oral cortisone therapy.

A 32-year-old female with skin and eye lesions considered to be those of sarcoidosis, showed a moderate improvement when treated with intramuscular ACTH combined with cortisone suspension applied topically to the eyes. Several reports of the successful control of this disease have appeared.[60]

Ulcerative Colitis

A 29-year-old female, suffering from recurrent attacks of ulcerative colitis with arthritis of the knees, of many years' duration, showed a moderate degree of improvement when treated intermittently with intravenous ACTH and oral cortisone. Several workers have reported gratifying results with the use of these agents in the more acute forms of this disease.[61]

Acute Pancreatitis

Two patients, both females, aged 9 and 26 years, with acute pancreatitis, responded favourably to ACTH given intravenously for 4 and 7 days respectively. In the latter case, the patient was severely shocked and pulseless and appeared to be in a moribund state; the use of ACTH was considered to have been life-saving. Such cases have been reported.[62]

Caustic Soda Poisoning

In 2 patients suffering from acute caustic soda poisoning, the use of intravenous ACTH for 6 days followed by oral cortisone for 2 weeks in the one and of intramuscular ACTH for a week in the other, afforded marked relief in respect of the pain and dysphagia. Sufficient time has not yet elapsed to judge whther cicatricial obstruction of the oesophagus will have been prevented by means of this therapy.

Diseases Treated Successfully with ACTH or Cortisone as Reported from Other Sources

A considerable number of diseases and abnormal conditions, not included in the present report, have responded favourably to treatment with ACTH or Cortisone. These are classified and listed below:

Endocrine and Metabolic Disorders

Waterhouse-Friderichsen syndrome,[63] adjunct to surgical operations involving the pituitary,[64] congenital adrenocortical hyperplasia (pseudo-hermaphroditism and virilization in females, macrogenitosomia praecox in males),[65] adrenocortical hypertension,[66] congenital hypoglycaemia,[67] essential glycogenosis (van Gierke),[68] anorexia nervosa,[69] non-tropical sprue (idiopathic steatorrhoea),[70] nephrotic syndrome,[71] toxaemias of pregnancy and eclampsia,[72] thyrotoxic crisis,[73] post-menopausal myopathy,[74] post-operative and post-traumatic anuria,[75] Sjogren's disease.[76]

Infections, Infestations, Intoxications, Infiltrations and Injuries (in conjunction with appropriate specific therapy)

General peritonitis,[77] severe bacteraemias and toxaemias,[78] typhoid fever,[79] trichinosis,[80] tuberculous meningitis,[81] tenosynovitis and bursitis (traumatic and infective)[82] interstitial cystitis,[83] severe burns,[84] silicosis and berylliosis,[85] Loeffler's eosinophillic syndrome,[86] snake bite poisoning and arachnidism.[87]

Allergic and Skin Disorders[9, 51]

Hay fever, angioneurotic oedema, urticaria and serum sickness, pemphigus foliaceous,[88] erythema multiforme exudativum (Stephens-Johnson syndrome),[89] herpes zoster,[90] post-herpetitic neuralgia,[91] post-irradiation laryngeal oedema,[92] alopecia universalis.[93]

Eye Diseases[52]

Sympathetic ophthalmia, optic neuritis, retrobulbar neuritis, secondary glaucoma, syphilitic keratitis, nodular episcleritis, Eale's disease, penetrating wounds.

Blood Diseases

Acquired haemolytic anaemia,[94] Cooley's anaemia,[95] periodic neutropenia,[96] sickle cell anaemia.[97]

Discussion

According to the results observed in this series of cases, it is apparent that the conditions which react favourably to ACTH and cortisone may be classified into 4 classes.

Class 1: Acute or subacute conditions in which a single course of treatment suffices to induce a permanent remission. In these the presence of the injurious causative factor is self-limited (e.g. in acute infections, certain drug eruptions, traumatic and surgical shock and also corrosive poisoning and burns). The duration of the course of treatment needed may vary from a few hours to several weeks.

Class 2: Acute or subacute conditions in which repeated courses of treatment are required, each inducing a temporary remission. In these the presence of the injurious factor, which may be extrinsic or intrinsic, is temporarily self-limited (e.g. the allergies, bronchial asthma, gout, iritis, certain dermatoses).

Class 3: Chronic conditions in which continuous treatment is needed for an indefinite period. Remissions, other than those occurring naturally, are not induced by treatment. The injurious causative factor is more or less permanently present. Cessation of treatment is almost invariably followed by a relapse (e.g. rheumatoid arthritis, systemic lupus erythematosus, periarteritis nodosa, scleroderma, pemphigus, exfoliative and atopic dermatitis).

Class 4: Endocrine disorders of the hypofunctioning or hyperfunctioning type. In these either substitution or suppression is needed permanently. Cessation of treatment is invariably followed by relapse. Small dosage usually suffices (e.g. Addison's disease, hypopituitarism, adrenocortical hyperplasia).

Conclusions

In conclusion, I should like to state that in my opinion the interest and enthusiasm shown by the medical profession in the use of these new therapeutic agents has been fully warranted. With the exercise of sound judgment in their application, experience has shown that the use of these hormones must be considered safe therapy. To my mind, the publicity which has been given to the dangers inherent in their use is largely unjustified and has often had the unfortunate effect of deterring the patient from accepting, or the doctor from prescribing this treatment, in cases where otherwise distinct benefit might have been derived.

These agents are natural biological products and the indications for their use have been based upon sound physiological principles, supported by carefully controlled experimental observations. In fact, their value for the control of certain diseases was predicted many years before they actually became available for clinical study and, as such, their present use cannot be regarded as the result of an accidental discovery.

It is admittedly difficult to conceive how the adrenocorticoid hormones are able to exert a favourable influence on such a wide variety of seemingly unrelated diseases, and one might be led to suspect that their mode of action

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is pharmacological rather than biological. However, recent researches [9] of fundamental importance have revealed that in certain diseases which react favourably to ACTH or cortisone therapy, such as lymphoma, rheumatoid arthritis and asthma, although there is no evidence of adrenocortical insufficiency, yet there is nevertheless a demonstrable derangement in adrenocorticoid metabolism. These findings indicate that the use of the same hormonal therapy for different and clinically unrelated diseases may nevertheless be rational.

With the introduction of these new biological agents, it is evident that we have entered a new era in therapeutics, in which the emphasis is on the host rather than on the irritant. Since their biological effects concern growth and mental processes, it is not beyond the realms of possibility that, in the near future, two of the great scourges of mankind, namely, cancer and mental disease, may be brought under control by further developments along these lines.

ADDENDUM

In the case of rheumatic fever showing slight improvement with ACTH therapy, referred to in Table 2, subsequent studies have revealed the fact that this patient is afflicted with systemic lupus erythematosus. The 50-year-old patient considered to have had lymphosarcoma, referred to in Table 14 and described in the text, has recently been shown to be suffering from chronic lymphatic leukaemia.

* * * *

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[The remaining papers read at the Plenary Session of the Johannesburg Medical Congress, devoted to Cortisone and ACTH, together with additional contributions, will be published in the next issue of the *Journal*.—*Editor*.]

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An Investigation* concerned with the bacteriology of vaginal flora following the use of internal tampons was undertaken at the request and with the co-operation of the visiting gynaecologists to a London women's hospital.

It is gratifying to find that this investigation confirms earlier work carried out in America and gives further support to the claim that Tampax can be confidently recommended as a convenient, comfortable and *safe* form of sanitary protection.

* *Tampax tampons were used in this investigation.*

EXTRACTS FROM THE REPORT:—

★ "Smears and cultures taken before and after each period showed no appreciable change in the bacterial flora of the vagina."

★ "None of the volunteers acquired monilia or trichomonal organisms during the period of study or developed erosions or vaginitis as a result of using the internal tampon."

★ "There was no aggravation of the condition or delay in healing following the use of tampons in the patients who had cervical erosions."

★ "In each case the underlying cause responded to treatment, and did not recur, which proves that the internal tampon does not act as an irritating foreign body."

★ "The rate of healing compared favourably with four control cases in which the perineal pad was used."

★ "The glycogen content was uninfluenced by the use of tampons."

★ "There was no appreciable alteration in the pH in the pre- and post-menstrual phases."

★ "Volunteers who had not previously used tampons stated that they did not cause the irritation usually found with the perineal pad."

★ "There was no evidence that vaginal tampons are prejudicial to health."

British Medical Journal, 1, 24 (1952

Literature and professional samples of Tampax will be sent on request

LENSVELT & COMPANY LIMITED P.O. BOX 2651 JOHANNESBURG

Coryza and other Winter Ailments— Simplified Prophylaxis

Immunisation against the common cold and allied respiratory disorders is still an imperative need. It concerns patient and doctor alike.

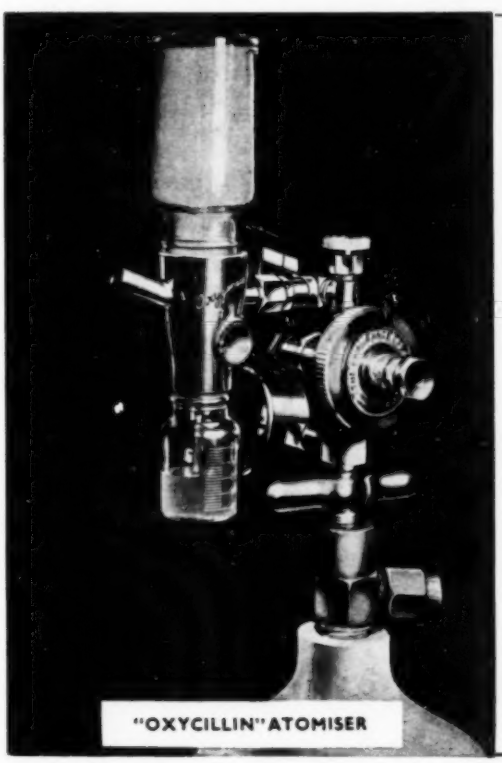
While it may be true that no known prophylactic is certain to succeed in every case a long experience here and abroad has proved that a very high percentage of success is obtainable through the use of 'ANTI-BI-SAN'.

'ANTI-BI-SAN' also has the great advantage that its administration is oral and brief: altogether seven small tablets are taken over three consecutive days. Nothing could be simpler. The resulting immunity, where established, starts one week after the course is finished and lasts for about three months.

'ANTI-BI-SAN' may be given to children and adults: it is absolutely safe and side-reactions are very rare. For further details about this valuable immunising product please write to the Distributors:—

'ANTI-BI-SAN'

FASSETT & JOHNSON, LTD., 72/80 Smith Street, Durban.



"OXYCILLIN" ATOMISER

Oxygenaire (South Africa) (Pty.) Ltd.

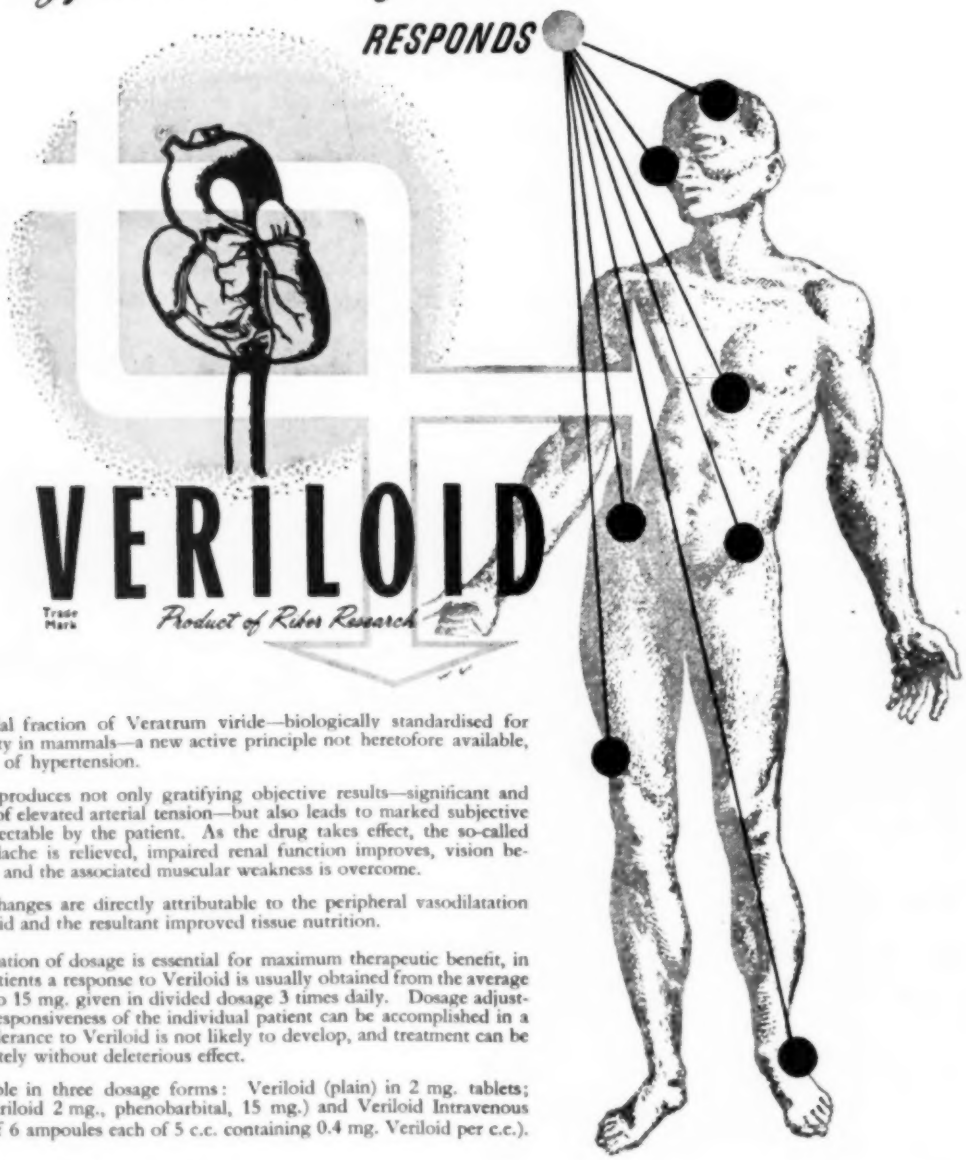
THE "OXYCILLIN" ATOMISER

THE "OXYCILLIN" ATOMISER ADMINISTERS OXYGEN AND PENICILLIN IN AEROSOL FORM. IT IS SPECIALLY DESIGNED FOR USE WITH OXYGEN TENTS OR ATTACHMENT TO AN OXYGEN INHALER. IT ADMINISTERS A DRY VAPOUR IN A FINE STATE OF SUBDIVISION AND EXTENSIVE RESEARCH HAS PROVEN THAT THE "OXYCILLIN" FULFILS ALL THE REQUIREMENTS FOR EFFECTIVELY PRODUCING PENICILLIN AEROSOL IN A STATE READILY ABSORBABLE.

THE UNIT IS ATTACHED TO A TWO-STAGE OXYGEN REGULATOR AND A CONTROL KNOB ENABLES THE SOLUTION TO BE GIVEN FOR SPECIFIC PERIODS WHILST OXYGEN IS GIVEN CONTINUOUSLY. A FINELY CALIBRATED SOLUTION CONTAINER ENSURES ACCURATE DOSAGE.

Enquiries:
53 Third Street, Bezuidenhout Valley, Telephone: 24-6936, Johannesburg

The Hypertension Syndrome



VERILOID

Trade Mark

Product of Riker Research

A potent alkaloidal fraction of Veratrum viride—biologically standardised for hypotensive activity in mammals—a new active principle not heretofore available, for the treatment of hypertension.

Veriloid therapy produces not only gratifying objective results—significant and sustained control of elevated arterial tension—but also leads to marked subjective benefit readily detectable by the patient. As the drug takes effect, the so-called hypertension headache is relieved, impaired renal function improves, vision becomes more clear, and the associated muscular weakness is overcome.

These beneficial changes are directly attributable to the peripheral vasodilatation induced by Veriloid and the resultant improved tissue nutrition.

While individualisation of dosage is essential for maximum therapeutic benefit, in the majority of patients a response to Veriloid is usually obtained from the average daily intake of 9 to 15 mg. given in divided dosage 3 times daily. Dosage adjustment to suit the responsiveness of the individual patient can be accomplished in a week or two. Tolerance to Veriloid is not likely to develop, and treatment can be continued indefinitely without deleterious effect.

Veriloid is available in three dosage forms: Veriloid (plain) in 2 mg. tablets; Veriloid—VP (Veriloid 2 mg., phenobarbital, 15 mg.) and Veriloid Intravenous Solution (boxes of 6 ampoules each of 5 c.c. containing 0.4 mg. Veriloid per c.c.).

Literature sent on request.

RIKER LABORATORIES AFRICA (PTY.) LTD. P.O. Box 1355, Port Elizabeth

2844-1

Provincial Administration of the Cape of Good Hope

HOSPITALS DEPARTMENT

VACANCIES: MEDICAL STAFF

Applications are invited from registered medical practitioners for appointment to three posts of medical practitioner, Grade A (2 Anaesthetists and 1 Department of Orthopaedics) on the staff of the Provincial Hospital, Port Elizabeth, with salary at the rate of £500—£600—£660—£720 per annum.

In addition to the rate of pay indicated, a variable cost-of-living allowance at rates prescribed from time to time by the Administrator of the Province, is payable. (Current rates: Single, £100 per annum; Married, £320 per annum.)

The privileges of free board, quarters and laundering are not attached to these posts.

The conditions of service are prescribed by the Hospital Board Service Ordinance No. 19 of 1941 (Cape) and the regulations framed thereunder.

Applications must be made on the prescribed form (Staff 23), which is obtainable from the Medical Superintendent of the Provincial Hospital, Gipson Road (P.O. Box 80), Port Elizabeth, to whom applications must be addressed to reach his office as soon as possible.

Port Elizabeth
12 February 1953 (3499)

Provincial Administration of the Cape of Good Hope

HOSPITALS DEPARTMENT

VACANCY: HONORARY MEDICAL STAFF

Applications are invited from registered medical practitioners under the age of 60 years for appointment to the post of Honorary Registrar to the Department of Gynaecology and Obstetrics at the Provincial Hospital, Port Elizabeth.

The appointment is subject to the Hospital Ordinance No. 18 of 1946 (Cape), as amended, and the rules and regulations of the Department.

Applications containing full particulars of qualifications and experience, must be addressed to the Medical Superintendent of the Provincial Hospital, Gipson Road (P.O. Box 80), Port Elizabeth, to reach his office as soon as possible.

Port Elizabeth
12 February 1953 (3499)

Springs Industrial Benefit Society

Applications are invited from registered medical practitioners to attend to members of the Springs Industrial Benefit Society in the Springs, Brakpan and Benoni areas.

Particulars obtainable from Secretary, P.O. Box 488, Springs.

Before applying for this appointment, practitioners are advised to communicate with the Honorary Secretary, East Rand Branch (M.A.S.A.), 9 Elgin House, Benoni.

Assistant Wanted

Assistant wanted in general practice. Natal Midlands. Own car. Reply re conditions, etc. to 'A. P. T.', P.O. Box 643, Cape Town.

Institute of Basic Medical Sciences

LECTURES AND DEMONSTRATIONS IN ANATOMY, APPLIED PHYSIOLOGY AND PATHOLOGY, OCTOBER 1953—JANUARY 1954

A full-time Course of Lectures and Demonstrations in the above subjects will be held at the Institute from 5 October 1953—1 January 1954. Applications for this Course will be strictly limited.

Fee - £63 . 0 . 0

Closing date for applications is Friday, 3 April 1953.

LECTURES IN ANATOMY, APPLIED PHYSIOLOGY AND PATHOLOGY OCTOBER 1953—JANUARY 1954

A course of Lectures only in the above subjects will be held at the Institute from 5 October 1953—1 January 1954. The Lectures will be held in the mornings from Monday to Friday each week.

Fee - £36 . 15s . 0

Full information and application forms for these courses may be obtained from Mr. W. F. Davis, Secretary, Institute of Basic Medical Sciences, Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2. (Holborn 3474).

Municipality of White River

VACANCY: PART-TIME MEDICAL OFFICER OF HEALTH

Applications are hereby invited for the position of part-time Medical Officer of Health at a remuneration of £60 per annum.

Applicants must be bilingual and must furnish full particulars of their qualifications and experience.

The successful candidate will be required to enter into an agreement with the Council, detailing the duties and terms of appointment, particulars of which may be obtained from this office.

Applications endorsed 'Part-time Medical Officer of Health' must reach the undersigned not later than noon on Thursday, 16 April 1953.

J. B. H. Rabie
Town Clerk

Municipal Offices
White River
16 February 1953 (866)

De Beers Consolidated Mines, Limited, Benefit Society

APPOINTMENT OF MEDICAL OFFICERS

Applications are invited from registered practitioners as Medical Officers to the above Society.

Applications stating qualifications, experience, etc., should be addressed to the Secretary, P.O. Box 616, Kimberley, from whom copies of contract may be obtained by *bona fide* applicants.

Duties to commence on 1 April 1953.

[This appointment has the approval of the Medical Association.—*Editor.*]

The Medical Association of South Africa : Die Mediese Vereniging van Suid-Afrika

AGENCY DEPARTMENT : AGENTSKAP-AFDELING

DURBAN

112 Medical Centre, Field Street. Telephone 2-4049

PRACTICES FOR SALE : PRAKTYKE TE KOOP

(PD13) Natal Lower South Coast practice, near Pondoland border, suitable for retired doctor. Area developing and large Police holiday camp in vicinity. Excellent climate and very good fishing. Premium required £400, includes good stock of drugs and dressings, instruments and dispensary furniture. House for sale £1,800, including stand of one-third morgen. Bond available. For immediate sale. Owner having taken a full-time appointment.

(PD14) Non-European dispensing practice in rapidly expanding industrial and residential area, 11 miles from centre of coastal City. At present no night or after-hour calls, no week-end or surgical work undertaken. Practice could be improved if run on a full-time basis, otherwise ideal as a subsidiary practice. Turnover for twelve months ended 31 June 1952 averaged £170 per month. Total expenses including car and travelling expenses £50 to £60 per month. Premium £750 including drugs, instruments and furniture.

(PD15) General practice established 1941 at pleasant residential and seaside resort about 10 miles south of Durban. Annual income approximately £1,000. No major surgery, minimum of minor surgery and only emergency midwifery being done at present. Brick house with consulting room attached, for sale at £5,250. Owing to ill health owner wishes to retire early in 1953. Premium £1,250 including drugs, surgery and dispensary furniture.

(PD18) Natal Midlands. Excellent prospects in rapidly developing area. General mixed practice. Seller going overseas. Premium £1,500 includes surgery furniture, fittings, instruments. Total gross receipts for 1950, £2,691; 1951, £2,709; 1952, £2,573. Ideal climate and sporting facilities. For immediate sale.

ASSISTENTE/PLAASVERVANGERS VERLANG ASSISTANTS/LOCUMS REQUIRED

(130) Natal Midlands. Assistant required as soon as possible. Salary £90 per month if assistant uses own car. £75 per month if car is to be provided. Must have had experience of non-European patients. Hospital town. District surgeon appointment held but very little travelling and a minimum of night calls. Practice centralized at surgeries attached to principal's house.

(132) Durban. Locum required as soon as possible for 3 months in well-established general practice. Possibility of assistantship. Salary to be discussed with the principal.

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JOHANNESBURG

Medical House, 5 Esselen Street. Telephone 44-9134-5, 44-0817
Mediese Huis, Esselenstraat 5. Telefone 44-9134-5, 44-0817

PRAKTYKE TE KOOP : PRACTICES FOR SALE

(Pr/S34) Progressive Transvaal dispensing practice. Average gross income £3,500 per annum. Excellent surgical facilities. Premium required £2,500 and the following terms could be arranged: £1,250 deposit and the balance over a period of 18 months, starting 3 months after the cash payment. The premium includes drugs, furniture and fittings, estimated at £800. Two transferable appointments worth £230 per annum.

(Pr/S54) Established branch practice in Johannesburg. Annual income £1,000. Premium required £500. Very much scope for expansion.

(Pr/S60) Prescribing practice in Southern Rhodesia. Monthly income approximately £500. Very modern hospital. Will suit doctor interested in surgery and midwifery. Premium required £5,000, and terms will be accepted.

(Pr/S63) Goedgevestigde Vrystaatse praktyk. Medisyne word aangemaak. Jaarlikse inkomste £2,400. Premie verlang is £1,000 en sluit voorraad medisyne en spreekkamermeubels in. Goeie kanse vir uitbreiding.

(Pr/S66) Uitstekende O.V.S. praktyk. Medisyne word aangemaak. D.G. aanstelling. Jaarlikse inkomste £3,400. Geen slegte skulde. Premie verlang is £1,250 en sluit voorraad medisyne en apteekmeubels in. Lieflike moderne woonhuis kan oorgeneem word teen slegs £3,350, waarvan £750 deposito sal wees en balans op verband.

(Pr/S69) Entirely cash non-European practice in Johannesburg. Average monthly income £100. Considerable scope for expansion. No reasonable offer will be refused. Rooms to be shared with dentist.

(Pr/S68) Well-established non-European dispensing practice. Annual income £1,800. Premium required is £1,200, and includes drugs, furniture and fittings. This practice will most definitely suit a woman doctor too.

(Pr/S70) O.F.S. hospital town. Very well-established practice. One appointment. Average annual income £3,600. This outstanding practice is for sale at only £1,500, payable as follows: £1,000 cash and balance over 15 months. A most delightful home is for sale at only £4,000 and a large bond could be raised.

(Pr/S71) O.F.S. hospital town. Monthly income of £225 of which £150 cash. Excellent scope for expansion. Will suit doctor interested in surgery. No reasonable offer will be refused.

(Pr/S72) Johannesburg—Northern Suburbs. Income of £1,000 per annum. Practice and house must be sold together and most liberal terms will be arranged.

(P/O15) O.F.S. country practice. Half share in general practice. Annual income £7,000 plus, showing a net income of £2,000 for each partner. Premium £2,250. Please apply for details.

(Pr/S16) Half share in general practice in Southern Rhodesia hospital town. Average net share of each partner £4,600 p.a. Appointments worth £2,700 p.a. Premium and house on terms.

(P/O17) Randse hospitaaldorp. Helfte aandeel in goedgevestigde praktyk, met sterk kraam neiging. Inkomste sal ongeveer £3,000 per jaar beloop. Premie verlang is £4,000 en terme kan gereël word.

(P/O18) Vennootskap op O.V.S. goudvelde. Groot mynaanstelling. Versekerde inkomste van ongeveer £1,400 per vennoot per jaar en sal definitief vermeerder sodra hospitaal voltooi is. Premie £1,800 en terme kan gereël word.

• • • •

KAAPSTAD : CAPE TOWN

Posbus 643, Telefoon 2-6177 : P.O. Box 643, Telephone 2-6177

PRAKTYKE TE KOOP : PRACTICES FOR SALE

(895) Partnership share in practice of Specialist Physician. Details on application.

(1132) East Griqualand. Opportunity for highly lucrative unopposed practice. Rich European farming area bounded by large native territory. D.S. appointment. Beautifully built large 7-roomed house on 3 erven. New Diesel lighting plant fully automatic generating 230 volts. £4,000 required for house, lighting plant, stock of drugs. Easy terms.

(740) Large dispensing practice, mainly non-European. Average annual cash receipts approx. £5,200. £5,500 required for premium, drugs and surgery furniture. Details on application.

(1276) Large hospital town, solus practice. Cash income for 1952 was £3,831 11s. Premium required is £2,250 cash or £2,500 on terms. Excellent surgery furniture as well as instruments included.

(1115) Cape Town suburban practice. Details on application.

(1266) Noord-Kaaplandse hospitaaldorp. Praktyk met kontantontvangste ongeveer £5,300 jaarliks. Geen opposisie. Medisyne word toeberei. Premie verlang £2,500 (medisyne, spreekkamermeubels, ens. word ingesluit). Huis te koop teen £2,000. Terme in afbetaling kan gereël word.

(1279) Kaap Provinsie, Hawestad. Praktyk met inkomste van £3,700. Premie £3,500, apteekmeubels, ens. ingeslote. Huis moontlik te huur, teen £20 p.m. Uitstekende geleentheid vir uitbreiding.

(1280) Eastern Cape dispensing practice with a large native population. Gross receipts £3,151. Premium required £1,500 including drugs, fittings and furniture. Modern house for sale at £3,500.

ASSISTENTE/PLAASVERVANGERS VERLANG
ASSISTANTS/LOCUMS REQUIRED

(1256) Kaapse Middellande. Gedurende Maart of April, vir 3 weke. £2 12s. 6d. per dag plus vry losies en kartoelaag.
(1073) Klein-Karoo. Vanaf 11 Mei tot 11 Julie 1953. £2 10s. per dag, losies en motor- of motoronkoste word voorsien. Goeie geleentheid om snykundige ondervinding op te doen in 'n vennootskapspraktyk.
(861c) Karoo. Assistent vir 2 maande in hospitaaldorp.
(979) Boland hospital town. Assistant with view to partnership. Car provided. Salary £75 per month. Single man preferred.
(1299) Northern suburb. From 8 May 1953 for ± 3 months. Salary offered £75 plus £5 petrol allowance. Single man to live in.

FOR SALE

(1079) HUMAN SERUM ALBUMEN imported from U.S.A., fully potent for further 18 months, held in refrigeration at Cape Town. Indicated for use in any condition in which the blood protein is reduced.
Below oedema levels can be restored to normal within 12 hours.
(1020) Port Elizabeth. E.C.G. Sanborn viso-cardiette: portable 11 Selector Lead all-mains' model in perfect condition. Payment could be made in instalments.

CONSULTING ROOMS WANTED

(1082) Specialist requires consulting rooms in Central Cape Town for a few hours daily. Wishes to share waiting room and services recep'ionist. (Quote also **1136** and **1228**).

DOCTOR'S RESIDENCE FOR SALE

This is a double storied eight-roomed home with large grounds situated in a most desirable part of Rondebosch which should prove attractive to any practitioner who wishes to own a home of this quality. Arrangements to view should be made with the local Agency Manager, Medical House, 35 Wale Street, Cape Town.

Public Service Commission

VACANCIES IN THE PUBLIC SERVICE

1. The attention of medical practitioners, registered with the South African Medical and Dental Council, is drawn to an advertisement appearing in the *Government* and *Provincial Gazettes* of this week, inviting applications for the undermentioned posts:

Post	*Department*	*Salary Scale*
Thoracic Surgeon	Health (Durban and Retreat)	£1,650 (fixed).
Anaesthetist	Health (Durban and Retreat)	£1,650 (fixed).
Specialist Physician	Health (Durban)	£1,650 (fixed).
Medical Officer	Health (Mental Hospital Service)	£900 x 50—1,150.
Medical Officer	Health (Kimberley and Retreat)	£900 x 50—1,150.
Assistant Pathologist	Health (Cape Town and Durban)	£900 x 50—1,050.

2. In addition to salary a cost-of-living allowance at the rate of £320 per annum (married) and £100 per annum (single) is payable at present.
3. It is emphasized that full and detailed particulars of qualifications and previous experience must be furnished but original certificates and testimonials should not be submitted. Application forms (Z.83 and P.S.C.8 (a)) are obtainable from the Secretary, Public Service Commission, Pretoria, to whom filled-in forms must be addressed.
4. The closing date for the receipt of applications is 28 March 1953. (39931)

Dermatome for Sale

Padgett Dermatome, complete with 2 blades in strong case. Good working order. Price £25. Write 'A. P. U.', P.O. Box 643, Cape Town.

Vakante Poste vir Distriksgeneeshere

Aansoeke om ondergenoemde poste van distriksgeneeshere met vermelding van land van geboorte, kwalifikasies, ondervinding, vorige en teenswoordige betrekkings en die vroegste datum waarop diens aanvaar kan word, indien aangestel, word ingewag deur die Sekretaris van Gesondheid, Posbus 386, Pretoria, en moet hom voor of op 25 Maart 1953, bereik. Getuigskrifte (afskrifte) kan gestuur word, maar die Minister van Gesondheid wil dit goed laat verstaan dat 'n kandidaat as gediskwalifiseer beskou word as hy regstreeks of onregstreeks steun vir sy benoeming werf.

Die aanstelling is deeltyds en private praktyk word toegelaat.

Applikante moet ook vermeld of hulle albei amptelike tale ken, asook of hulle melaatsheid en veneriese siekte kan diagnoseer, en die moderne binneaarse en ander geneeskundige metodes by die behandeling van veneriese siektes kan toepas.

Applikante moet ook vermeld of hulle ondervinding as mediese gesondheidsbeamptes of in 'n soortgelyke hoedanigheid gehad het. As om meer as een pos aansoek gedoen word moet 'n afsonderlike aansoek ten opsigte van elkeen ingedien word.

Plek	*Salaris per jaar*	*Toelae vir medisyne per jaar*
Kaapprovinsie:	£	£
Tabankulu	350	10
Villiersdorp	90	20
Libode	280	15
Lambertsbaai	100	20
Alicedale	100	20
Franschhoek	359	20
Transvaal:		
Villa Nora	350	25
Marikana	200	30
Alberton	200	*
Oranje-Vrystaat:		
Excelsior	200	40
Natal:		
Ngotshe (Louwsburg) ..	500	50
†Ladysmith	500	30

*Medisyne kragtens kontrak verskaf.
†Hierdie aanstelling is onderworpe aan opsegging met een maand kennisgewing in plaas van die gewone drie maande kennisgewing.

Die salaris dek alle en routine-dienste dog reistoelae teen 1s. per myl vir alle afstande wat buite 'n omtrek van drie myl vanaf die standplaas afgeleë is, nagverblyf teen 15s. en bykomende vergoeding vir sekere ander dienste word betaal, asook gelde vir bywoning van hofsitting en geregtelike lykskouings ooreenkomstig die skaal van die Departement van Justisie.

Aansoeke- en kopieë van kontrakvorms word op aansoek verstrek.

(39914)

The Stanwool Benefit Society

Applications are hereby invited from registered medical practitioners for the post of part-time Medical Officer to the above Benefit Society in Harrismith.

Applications must reach the Secretary not later than 31 March 1953.

Further information may be obtained from the Secretary, P.O. Box 121, Harrismith.

[This appointment is approved by the S.A. Medical Association.—*Editor.*]

Transvaal Provincial Administration

VACANCIES: TRANSVAAL PUBLIC HOSPITALS

Applications are invited from suitably qualified candidates for the undermentioned posts at Public Hospitals in the Transvaal.

Applications should be addressed to the Medical Superintendents of the undermentioned Hospitals concerned and should contain full particulars as to the age, professional and academic and language qualifications, experience and conjugal status of the applicant and should further indicate the earliest date upon which duties can be assumed. Copies, only, of recent testimonials to be attached.

Cost-of-living allowance payable at present to full-time employees:

	Cost-of-living Allowance	
Salary	*Married*	*Single*
Over £350 per annum	£320 per annum	£100 per annum

Full-time employees receive in addition to their salaries and cost-of-living allowance, the following privileges:

Leave and rail concession.

Successful candidates will be required to submit satisfactory certificates as also to submit to a medical examination at the hospital concerned.

Application forms are obtainable from any Transvaal Provincial Hospital or the Provincial Secretary, Hospital Services Branch, P.O. Box 2060, Pretoria.

The closing date of applications for undermentioned posts will be 16 March 1953:

Hospital	*Post*	*Emoluments*	*Remarks*
Johannesburg Hospital Board and the University of the Witwatersrand	Full-time Assistant Surgeon (1)	£1,200 x 50 1,500	Registered medical practitioner. Higher qualifications in surgery a recommendation. To commence duties on 1 April 1953, or as soon as possible thereafter. Temporary post only.
Witbank	Part-time General Practitioner (1)	£510 per annum	Registered medical practitioner. Three sessions per week. (39848)

University of the Witwatersrand, Johannesburg

HEALTH CENTRE AND UNIVERSITY CLINIC AT ALEXANDRA TOWNSHIP, JOHANNESBURG

VACANCY FOR ASSISTANT MEDICAL OFFICER

Applications for this vacancy are invited from suitably qualified medical practitioners.

Salary scale £900 × 50—£1,150, plus statutory cost-of-living allowance.

Duty to be assumed 1 April 1953.

Applications to be sent to Assistant Registrar, Medical School, Hospital Hill, Johannesburg, before 21 March 1953. (1259)

Radiographer Required

Radiographer required for private radiological practice in Johannesburg. Salary according to experience. Reply to 'A. P. S.', P.O. Box 643, Cape Town.

For Sale

Old-established physiotherapy practice in expanding Reef town, few miles from Johannesburg. Fully equipped treatment rooms, office, waiting room in central position. For details apply Physiotherapist, Box 8625, Johannesburg.

Siekefonds van die Suid-Afrikaanse Spoorweë en Hawens

AANSTELLING VAN KINDERSIEKTEKUNDIGE: PRETORIA

Aansoeke word van geregistreerde kindersiektekundiges ingewag vir aanstelling in die betrekking van kindersiektekundige, Pretoria, teen 'n salaris van £626 per jaar, plus die gelde en toelaes wat in die regulasies van die Siekefonds voorgeskryf word, en met die reg om privaat te praktiseer.

Die salaris is onderhewig aan wysiging in ooreenstemming met die sensus van Iede wat op 1 April elke jaar afgeneem moet word.

Die aanstelling geskied kragtens die regulasies van die Siekefonds, en opsegging van dienste is onderworpe aan vier maande kennisgewing deur een van beide partye.

Die suksesvolle applikant moet op Pretoria woon, diens aanvaar op 'n datum wat gereël sal word, en sy pligte ooreenkomstig die regulasies van die Fonds uitvoer.

Aansoeke moet die Distriksekretaris, Distriksiekefondsraad, Oos-Transvaal, Scheidingstraat, Pretoria, nie later nie as 25 Maart 1953 bereik, en applikante moet die volgende vermeld:

1. Volle naam.
2. Kwalifikasies (waar en wanner verkry).
3. Ondervinding (waar en wanneer verkry en opgedoen).
4. Datum van geboorte.
5. Land van geboorte.
6. Getroud of ongetroud.
7. Of ten volle tweetalig.
8. Of Suid-Afrikaanse burger.
9. Watter staatsbetrekking, indien enige, beklee word.

Werwing deur of ten behoewe van enige applikant stel so 'n applikant bloot aan diskwalifikasie.

Enige ander besonderhede wat verlang word, kan op aanvraag van die Distriksekretaris by bovermelde adres verkry word.

P. J. Klem
Hoofsekretaris

Johannesburg
7 Maart 1953

Witbank Coalfields Benefit Society

Applications are invited from registered medical practitioners for appointment as Medical Officer to any, or all, of the Society's Units, listed below, in the Witbank, Transvaal, district.

The Medical Officer will be required to provide his own consulting room, conveniently situated, and render ordinary medical and surgical treatment to members and their dependents (European), making at least two visits per week to the Mines, on each of which there is a consulting room.

1. Alpha Colliery.
2. Dunn's Engineering.
3. Klippoortjie Colliery.
4. Springbok Colliery.
5. Transvaal Navigation Colliery.
6. Van Dyk's Drift Colliery.
7. Witbank Consolidated Coal Mines.

Further details can be obtained from the Secretary, Witbank Coalfields Benefit Society, P.O. Box 26, Witbank, Transvaal. The closing date for the receipt of applications is 24 March 1953.

[This appointment has the approval of the Medical Association of South Africa.—*Editor.*]

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